Development of Gold(I)- and Indium(III)-Catalysed Reactions

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Abstracts

This thesis contains an introductory chapter to gold(I)- and indium(III)-catalysis, followed by five chapters outlining the research undertaken by the author during the duration of study.

Chapter 1 gives an introduction to gold(I)- and indium(III)-catalysis and, in particular, focuses on the reported literature on the development of the gold(I)-catalysed reactions of allenes.

Chapter 2 describes the research undertaken into the dehydrative thiolation of allenols, and the discovery of $InCl_3$ as a superior catalyst for this reaction compared to Au(I). The use of $InCl_3$ as a catalyst provided excellent regioselectivities of the desired 1,3-diene products in good to excellent yields. Several reactions were carried out using a gold(I) catalyst for comparison, but they consistently provided lower yields and poorer regioselectivities. Mechanistic studies outlining the differences between Au(I) and In(III) are also discussed.

Chapter 3 details the developments on the dehydrative reactions of allylic alcohols to form allylic ethers, with an In(III) *vs.* Au(I) comparison. These investigations show that $InCl_3$ can be used as a cheaper alternative to Au(I) for this reaction and, in some cases, outperforms Au(I). In particular, In(III) exhibited superior performance as a catalyst when substrates or nucleophiles contain pendent π bonds.

Chapter 4 presents the successful development of a mild protodeboronation reaction of boronic acids under gold(I)-catalysis. Additive free conditions and the use of "green" solvents provides a mild reaction with an excellent functional group tolerance. This method can be adapted for a regioselective *ipso*-deuteration technique which would be useful in labelling studies. Mechanistic investigations are also discussed.

Chapter 5 outlines a quick and efficient iododeboronation reaction which can be carried out in “green” solvents in under 10 mins, making this reaction potentially useful for radiolabelling studies.

Chapter 6 describes the first intermolecular gold(I)-catalysed chirality transfer hydroalkoxylation reaction of 1,3-disubstituted allenes. These reactions proceed with excellent regioselectivity and a high degree of chirality transfer. Mechanistic studies are also discussed.

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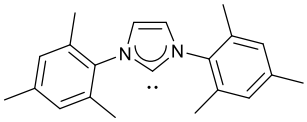
Table of Contents

Abbreviations

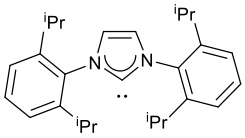
<	Less than
>	Greater than
α	Alfa
Å	Ångström (1×10^{-10} m)
β	Beta
δ	NMR Chemical shift (ppm)
γ	Gamma
°C	Degrees Celsius
Ac	Acetyl
AllylB(pin)	(Pinacalato)allylboron
APCI	Atmospheric pressure chemical ionisation
Ar	Aryl group
Bn	Benzyl
Bz	Benzoyl
BOC	*tert*-Butyloxycarbonyl
BDE	Bond dissociation energy
Br	Broad
^{t}Bu	*Tert*-butyl
BuLi	Butyl lithiums
cat.	Catalyst
cm	centimetre
conc.	Concentration
conv.	Conversion
CSP	Chiral Stationary Phase
d	Doublet

d.r	Diastereotopic ratio
DCE	Dichloroethane
DCM	Dichloromethane
DFT	Density functional theory
DMC	Dimethyl carbonate
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
EDA	Ethyl diazoacetate
EDG	Electron donating group
EDW	Electron withdrawing group
% ee	% Enantiomeric Excess
e.r	Enantiomeric ratio
EI	Electron ionisation
ESI	Electronspray ionisation
equiv.	Equivalent
Et	Ethyl
EtOAc	Ethyl Acetate
g	Gram
GC	Gas chromatography
h	Hours
Hz	Hertz
HPLC	High pressure liquid chromatography
HOMO	Highest occupied molecular orbital
HRMS	High resolution mass spectrometry

IMes	1,3-*Bis*(2,4,6-trimethylphenyl)imidazol-2-ylidene

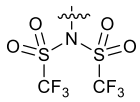


IPr	1,3-*Bis*(2,6-diisopropylphenyl)imidazol-2-ylidene



IR	Infra-red
J	Coupling Constant
LUMO	Lowest unoccupied molecular orbital
Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
Mp	Melting point
min	Minutes
mg	Milligram(s)
mL	Millilitre(s)
mmol	Millimole(s)
mol	Mole(s)
M	Molar (mol L^{-1})
MIDA	N-Methyliminodiacetic acid
MS	Molecular sieves
μW	Microwave
NBS	*N*-Bromosuccinimide
NBSH	2-Nitrobenzenesulphonylhydrazide

NCS	*N*-Chlorosuccinimide
ND	Not determined
NHC	N-Heterocyclic carbine
NIS	*N*-Iodosuccinimide
NMP	N-Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
NTf_2	*Bis*(trifluoromethanesulfonyl)amide



Nu	Nucleophile
OTf	Trifluoromethanesulfonate (Triflate)
OTs	*p*-Toluenesulfonate (Tosylate)
p	Para
Piv	Pivaloyl
PDC	Pyridinium dichromate
Ph	Phenyl
ppm	Parts per million
^{i}Pr	Isopropyl
Quant.	Quantitative
R_f	Retention Factor
r.t.	Room Temperature
s	Singlet
Temp.	Temperature

TBAF	Tetra-*n*-Butylammonium fluoride
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
THP	Tetrahydropyran
TMEDA	Trimethylethylenediamine
TMSCl	Trimethylsilyl chloride
TMSOTf	Trimethylsilyl trifluoromethylsulfonate
ToSMIC	Toluenesulfonylmethyl isocyanide
t	triplet

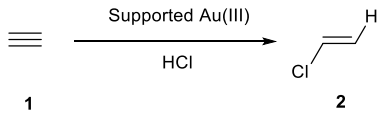
Chapter 1: Introduction

1.1 . History of Gold

Gold was one of the very first metals discovered by mankind and since then it has been highly valued by people throughout history. The ancient Egyptians were one of the first to manipulate gold. Inscriptions dating back to 2600 BC refer to gold. One of the most iconic pieces of gold is King Tutankhamun's death mask made around 1223 BC. The Egyptians not only used this metal to show wealth but believed it had magical properties. The use of gold meant that the mask did not tarnish or deteriorate over time due to its stability to air and moisture. This particular property means that gold has a wide variety of modern day applications including jewellery, currency, electrical and medicinal.

Due to gold's inertness, it was overlooked for many years by chemists, with other transition metals being favoured as catalysts. However, in recent years gold was found to have interesting chemical properties and as a result has become a widespread area of research.[1]

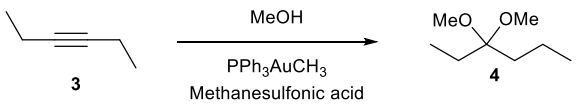
Gold catalysis can be dated back to the 1960's, however, it was in 1973 when the first milestone was reached by Bond *et al.* with the heterogenous catalytic hydrogenation of olefins over supported gold catalysts.[2] More than ten years later Hutchings reported the heterogenous gold catalysed hydrochloration of ethyne to form vinyl chloride. It was this seminal work which led to a much researched area of homogenous catalysis - the addition of nucleophiles to alkynes (Scheme 1.1).[3]



Scheme 1.1: Hydrochlorination of ethyne

However, these early publications focused on supported Au(III) catalysts and it was not until 1998 that homogenous Au(I) catalysis hit a major breakthrough with the work of Teles *et al.*

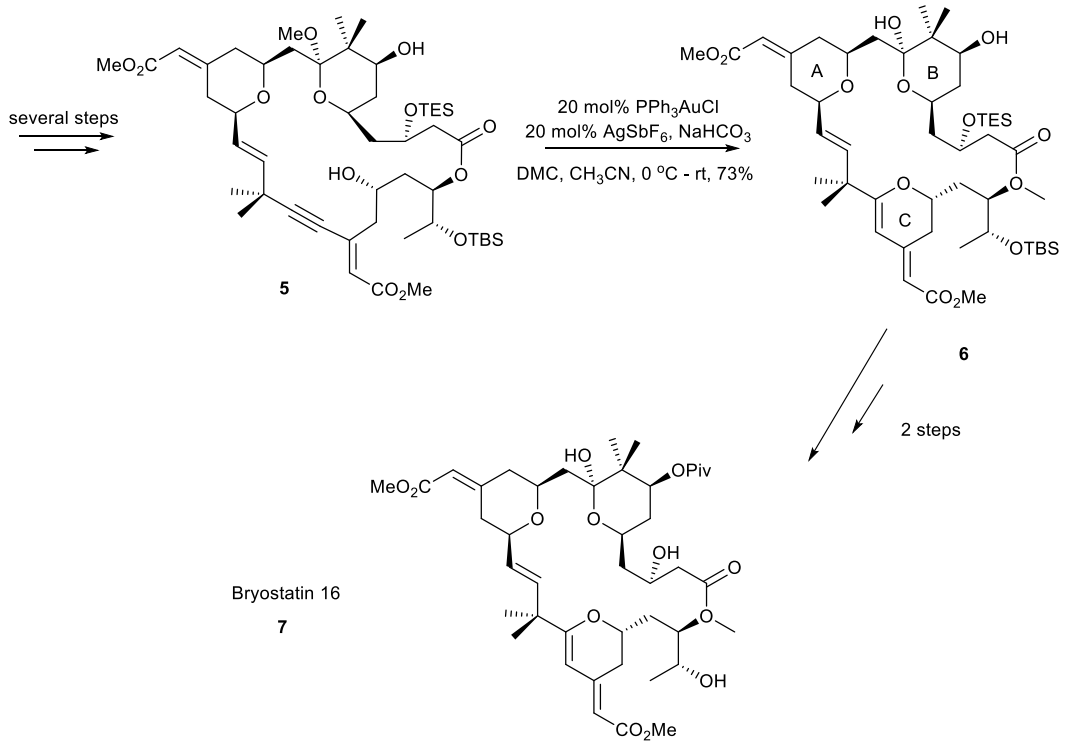
In 1998, Teles *et al*. found that cationic gold(I)-complexes were highly efficient for catalysing the addition of alcohols to alkynes (Scheme 1.2).[4]



Scheme 1.2: Au(I) catalysed addition of alcohols to alkynes

Previously, addition of alcohols to alkynes required the use of stoichiometric mercury salts. However, Teles' new discovery meant that the addition of alcohols to alkynes could now be carried out using mild conditions (20 – 50 °C, H^+ co-catalyst) with a non-toxic gold(I) complex. The active catalytic complex had the general form $[L\text{-}Au]^+$ where L can either be phosphane, phosphite or arsine. Furthermore, these catalysts were found to have an excellent turnover number, with $[PPh_3\text{-}Au]^+$ still active after 5000 turnovers.[4]

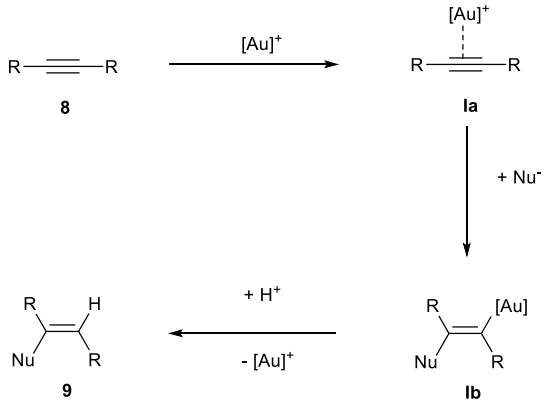
Since then, there have been numerous publications and gold catalysis now plays an important role in the synthesis of many bioactive molecules[5] including bryostatin 16 (**7**) which was successfully synthesised by the Trost group (Scheme 1.3).[6] Brysotatin 16 (**7**) occurs naturally in nature and is thought to have anti-cancer properties as well as potential to combat Alzheimer's disease.[5a] One of the key steps in the synthesis is a gold-catalysed 6-*endo*-dig cyclisation to form ring C, which shows the high chemoselectivity that can be achieved using gold catalysis (Scheme 1.3).[5a, 6]



Scheme 1.3: Total synthesis of Bryostatin 16 (**7**).

1.2 Bonding and Reactivity

Gold is a soft Lewis acid and as a result activates carbon-carbon multiple bonds towards nucleophilic attack as shown in Scheme 1.4. First, the gold complex coordinates to the π system to form an intermediate (**Ia**) which then undergoes an *anti*- nucleophilic attack to form complex **Ib**. Protodemetallation then produces product **9**. This same mechanism can also be applied to alkenes.[1a, 1f] It should be noted that intermediates such as **Ia** are not normally in the η^2 equilibrium structure and it is now widely accepted that slippage (η^2 to η^1) of the metal complex along the axis of the bound alkene or alkyne is part of the alkene or alkyne activation. It is thought that in these cases, electrophilicity is enhanced.[1b]



Scheme 1.4: Activation of C-C multiple bond

Carbophilic activation such as that of alkynes with gold (Scheme 1.4) involves the formation of a transition metal complex with the alkyne acting as a π ligand. In general, this usually involves the formation of a σ bond by overlapping the π system of the ligand with an empty metal orbital. A π interaction can then occur whereby the electron density from a filled metal d-orbital π back donates into an antibonding π^* orbital. As a result, the bond length of the alkyne increases, this effect can be observed through spectroscopic methods such as NMR.[7] However, in the case of Au(I) it has been shown, by computational studies, that π back bonding only accounts for one fifth of the bond dissociation energy (BDE). The largest contribution (over two thirds) comes from the σ interaction; meaning alkynes and alkenes are strong two electron donors but fairly weak π acceptors.[8] Since Au(I) deprives the π ligand of electron density and renders it electrophilic in nature, Au(I) is therefore considered a "π acid".[1b]

1.3 Au(I) Catalysts

Gold complexes predominately exist in two different oxidation states: Au(I) and Au(III), and both exhibit catalytic properties.[1b, 9] However, this thesis focuses mainly on gold(I)-catalysis and therefore only Au(I) homogenous catalysis will be discussed in this chapter.

In the case of Au(I), there is a strong preference for linear complexes, which generally have a coordination number of two.[10] Although rare, three and four coordinate Au(I) complexes are known (Figure 1.1).[11]

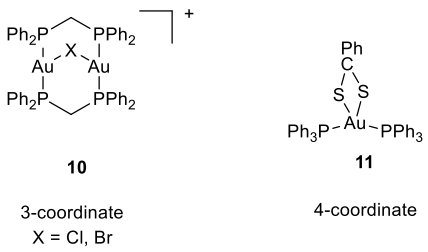
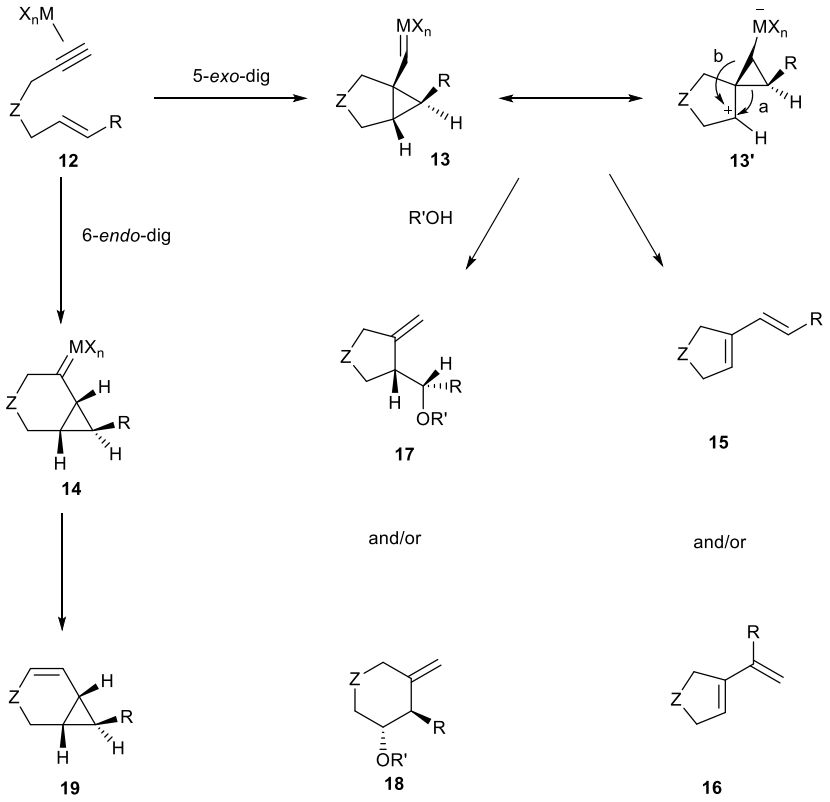


Figure 1.1: Examples of 3- and 4-coordinate gold complexes

The most well-known Au(I)-complexes are those which have phosphine ligands. Indeed, numerous papers have been published with regard to this subject. In 2004, Echavarren and co-workers found that for the *exo*- and *endo*-cyclisation of enynes (Scheme 1.5), cationic gold(I) complexes $[PPh_3Au]^+ X^-$ (where X = SbF_6^-, BF_4^-) had a much higher reactivity and selectivity over previously used transition metal catalysts[12] such as Pt(II), Pt(IV)[13] and Ga(III).[14]

The cyclisation of enynes firstly involves the coordination of the metal complex to the alkyne to form complex **12** (Scheme 1.5). Complex **12** can then proceed by either a 5-*exo*-dig or a 6-*endo*-dig cyclisation to form the metal cyclopropyl carbene complex **13** or **14** respectively. Skeletal rearrangement of α,ω-enynes may proceed via intermediates **13** (best envisioned via canonical form **13'**) to form conjugated dienes **15** (cleavage of bond a) and **16** (cleavage of bond b). Alternatively, attack of nucleophiles R'OH (alcohols or water) at **13** gives products of alkoxy- or hydroxycyclisation **17** and **18**.[12]



Scheme 1.5: Cyclisation of enynes

These gold(I) catalysts $[PPh_3Au]^+ X^-$ are usually formed *in situ* from $[PPh_3AuCl]/AgX$ ($X = SbF_6^-$) but it should be noted that Ag^+ ions does not catalyse this reaction.[12] Echavarren and co-workers further investigated this area by looking at different phosphine ligands: PPh_3, PCy_3, $P(C_6F_5)_3$ and $P(AsPh_3)$ were found to effectively catalyse the methoxycyclisation of a 1,6-enyne **12** in under 5 hours with excellent yields (82-88%). However, when the steric bulk was increased to P(*o*-tol)$_3$ or P(1-Naphth) the reaction time increased from 3 hours to over 18 hours. Further investigation involved testing complexes **20** and **21** (Figure 1.2) and surprisingly, the reaction time was decreased to under 30 minutes with good to excellent yields (82-97%).[15]

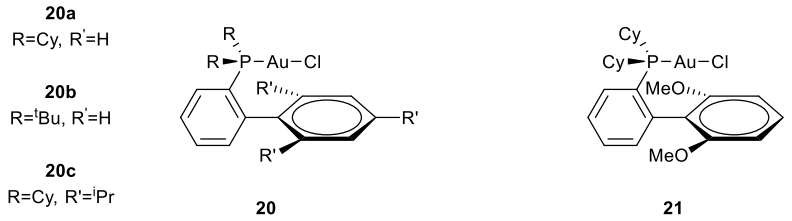
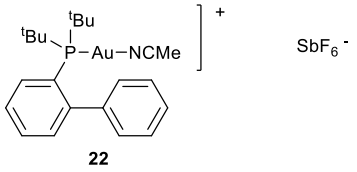


Figure 1.2: Gold pre-catalysts investigated by Echavarren and co-workers

Echavarren and co-workers proceeded to develop a silver free gold(I)-cationic complex **22** which is now commercially available (Figure 1.3) and often referred to as "Echavarren's catalyst". Studies have shown that these types of catalyst bind to alkenes to form air and thermally stable complexes.[16]



22

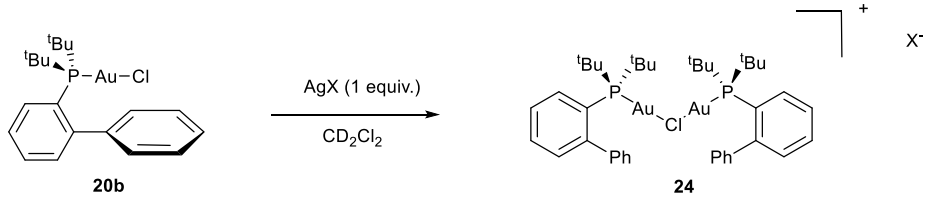
Figure 1.3: Echavarren's gold(I) cationic catalyst

In 2005, Gagosz and co-workers developed a highly efficient air-stable complex for the cycloisomerisation of enynes. This new complex by Gagosz also contains a phosphine ligand but uses NTf_2^- as the counterion in place of SbF_6^-. To synthesise the catalyst, they reacted Ph_3PAuCl with 1 equiv of $AgNTf_2$ to produce the desired catalyst **23** (Scheme 1.6). This new complex could be produced on a multigram scale and is now commercially available.[17]

Scheme 1.6: Synthesis of PPh_3AuNTf_2 by Gagosz

The advantages of catalysts **22** – **23** (Figure 1.3 and Scheme 1.6) are that they remove the practical difficulty of using silver salts which are often hygroscopic and cause difficulties in mass measurement.

There are several other problems associated with the use of silver salts. In 2013, Echavarren and co-workers described the formation of chloride-bridged digold complex **24** (Scheme 1.7). These complexes are formed when mixing the LAuCl precatalyst with a silver salt in the absence of a substrate in a non-coordinating solvent (Scheme 1.7).

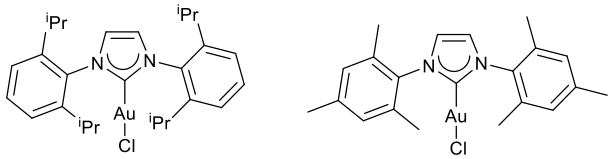


20b **24**

Scheme 1.7: Formation of chloride-bridged digold species

These complexes are significantly less reactive than the cationic gold(I)-complexes $[L\text{-}Au]^+ X^-$ and can therefore have an effect on the rate of the reaction. They therefore recommended premixing the substrate and the neutral LAuCl complex before adding the silver salt in order to minimise the formation of the unwanted chloride-bridged digold species **24**.[18]

NHC gold catalysts are one example where premixing of the LAuCl complex with the silver salt is required to obtain the active catalyst *in situ*. Although many NHC complexes exist, the two pre-catalysts used in this thesis were (IPr)AuCl **25** and (IMes)AuCl **26** (Figure 1.4).



25
(IPr)AuCl

26
(IMes)AuCl

Figure 1.4: Gold NHC complexes

NHCs exhibit a ground state electronic configuration, with the HOMO best described as a formal sp^2 hybridised lone pair (Figure 1.5) and the LUMO an empty *p*-orbital on C^2 (Figure 1.5). The nitrogen atoms are both electron-withdrawing through the σ bond and electron-donating through π-back donation. This is thought to enhance the stability of the NHC. The partial aromaticity of the NHC ligands in **25** and **26** is also thought to enhance the stability.

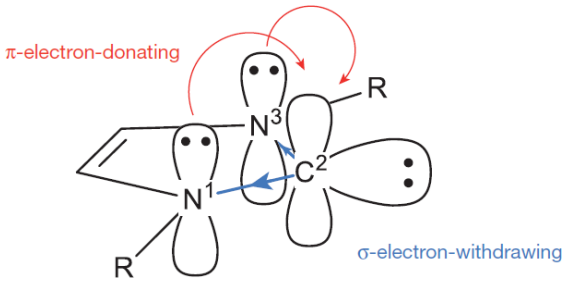


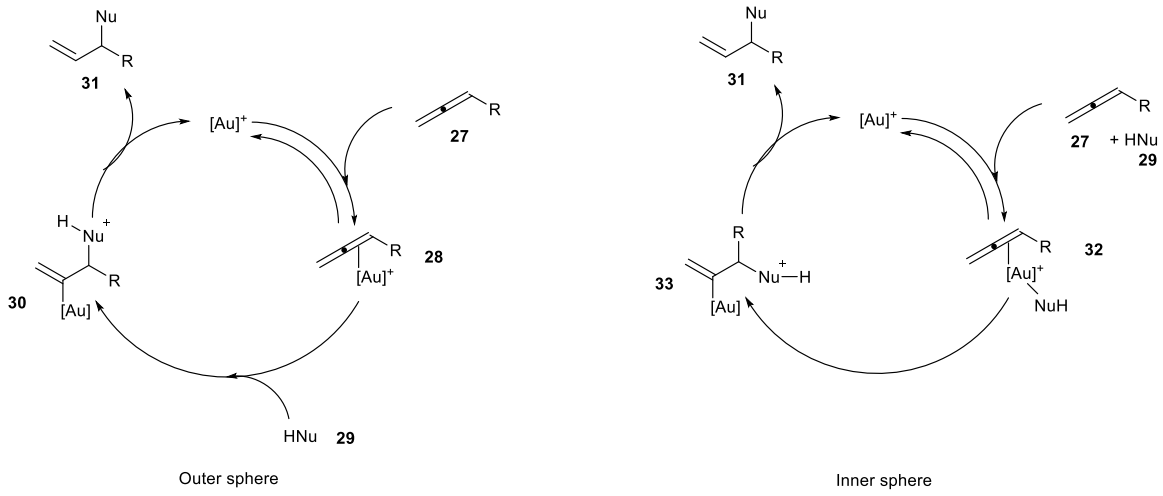
Figure 1.5: Structural features of NHC[19]

The lone pair in the plane of the heterocyclic ring renders these complexes nucleophilic and as such NHCs can act as σ donors and bind to a wide variety of metals.[19]

1.4 Reactivity of Allenes With Gold(I)

Allenes are valuable starting materials in organic synthesis as they have a wide variety of applications,[20] most notably in gold catalysis. As with alkenes and alkynes, allene carbon-carbon double bonds can be activated by gold to form new carbon-carbon bonds or carbon-heteroatom bonds in an intra- or intermolecular fashion.[21]

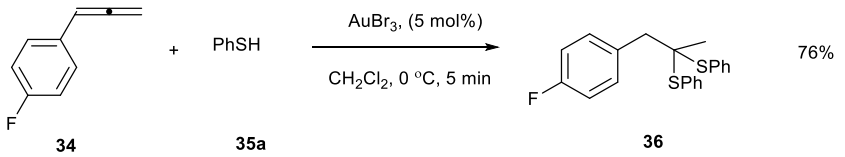
Many intermolecular reactions with allenes in the presence of a gold catalyst involve hydrofunctionalisation with nitrogen, oxygen and sulfur nucleophiles. These reactions were originally hypothesised to proceed by two different pathways: an outer sphere pathway (Scheme 1.8) where the cationic gold(I) complex acts as a π-acid (**28**) to induce addition of the nucleophile across the C-C bond (**30**), or an inner sphere mechanism where the tricoordinate gold complex **32** is formed by complexation of both the allene and the nucleophile (Scheme 1.8). Addition of the nucleophile to the allene proceeds from this complex (Scheme 1.8).[22]



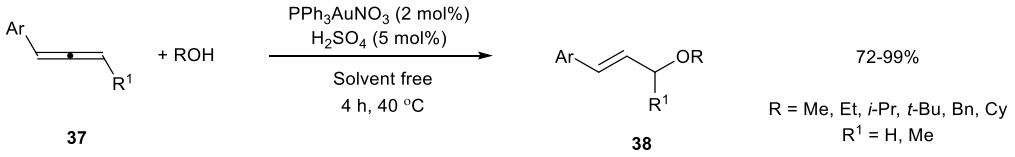
Scheme 1.8: Outer sphere and inner sphere mechanisms.

The hydroamination of allenes was originally thought to proceed *via* an inner sphere pathway as it was thought the nucleophile was involved in the rate determining step.[23] However, a kinetic study by Wang *et al*. found that the nucleophile was in fact not involved in the rate determining step and instead it was found that there is a first order dependence on the allene, suggesting it is involved in the turnover-limiting transition state.[22] It is also first order with respect to gold implying that the rate limiting transition state contains only one gold centre. These results show that an inner sphere mechanism

is unlikely and that the reaction is more likely to proceed through an outer sphere pathway. This was supported by computational studies.[22] Similarly, oxygen and sulfur nucleophiles were also thought to proceed through an inner sphere pathway.[23-24] However, recent computational studies suggest an outer sphere pathway is most likely.[25] These hydrofunctionalisation reactions proceed with good yields (Scheme 1.9 and 1.10).



Scheme 1.9: Hydrothiolation of allenes



Scheme 1.10: Hydroalkoxylation of allenes

However, although there are examples in the literature of gold-catalysed reactions with allenes such as those described above, unlike alkynes and alkenes, there is a lack of mechanistic understanding. This is easily explained by increasing selectivity problems when going from alkenes to allenes as shown in Figure 1.6. With alkenes it is a question of regioselectivity (Markovnikov or anti-Markovnikov orientation leading to constitutional isomers) and stereoselectivity of an addition reaction (*cis*- or *trans*-addition at possibly enantiotopic or diastereotopic faces of the double bond) leading to stereoisomers. With alkynes, as well as the problems associated with alkenes, there is an additional issue; that of chemoselectivity (single or double addition leading to different products). With allenes, as well as the problems of selectivity described above, there is also the issue of positional selectivity (which of the two orthogonal bonds will react in the case of single addition, again leading to constitutional isomers).[26]

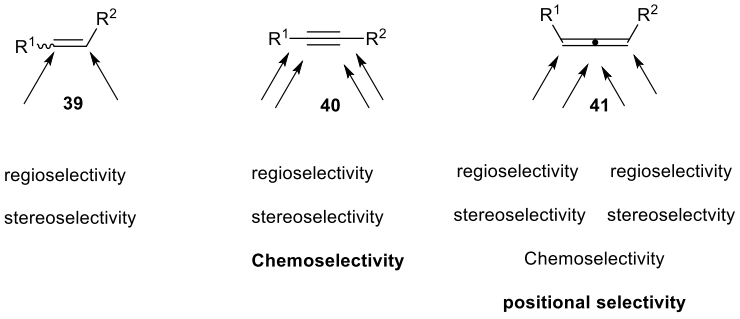


Figure 1.6: Selectivity issues going from alkenes to allenes

Since allenes possess this unique reactivity and a particular coordination mode to the cationic Au(I) metal centre, few mechanistic experimental investigations of nucleophilic addition exist. However, research involving computational studies in this area is increasing.

There are several coordination modes of allenes (Figure 1.7) to an Au metal centre which can be divided into two categories; η^2 complexes **Ic** which involve one of the two orthogonal bonds. The contribution of the two carbons varies depending on the substitution pattern of the allene which may lead to slipped structures of type **Ic'** or type **Ic''** where **Ic'** is favoured by electron-donating groups on the allene and **Ic''** is favoured by electron-withdrawing groups on the allene. The second category involves the Au complex coordinated to the central carbon of the allene leading to σ-allylic cations **Id**, zwitterionic carbenes **Id'** and finally η^1 coordinated bent allenes **Id''**.[27]

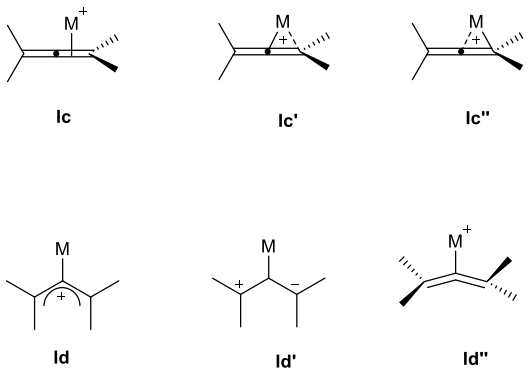


Figure 1.7: coordination modes of allenes

The coordination mode is an important factor in determining the stereochemical outcome. For example, in an axis-to-centre transfer, the stereochemical information is maintained

in species **Ic** and **Id''** but would be lost in **Id** possibly due to the three carbon atoms being in the same plane.[28]

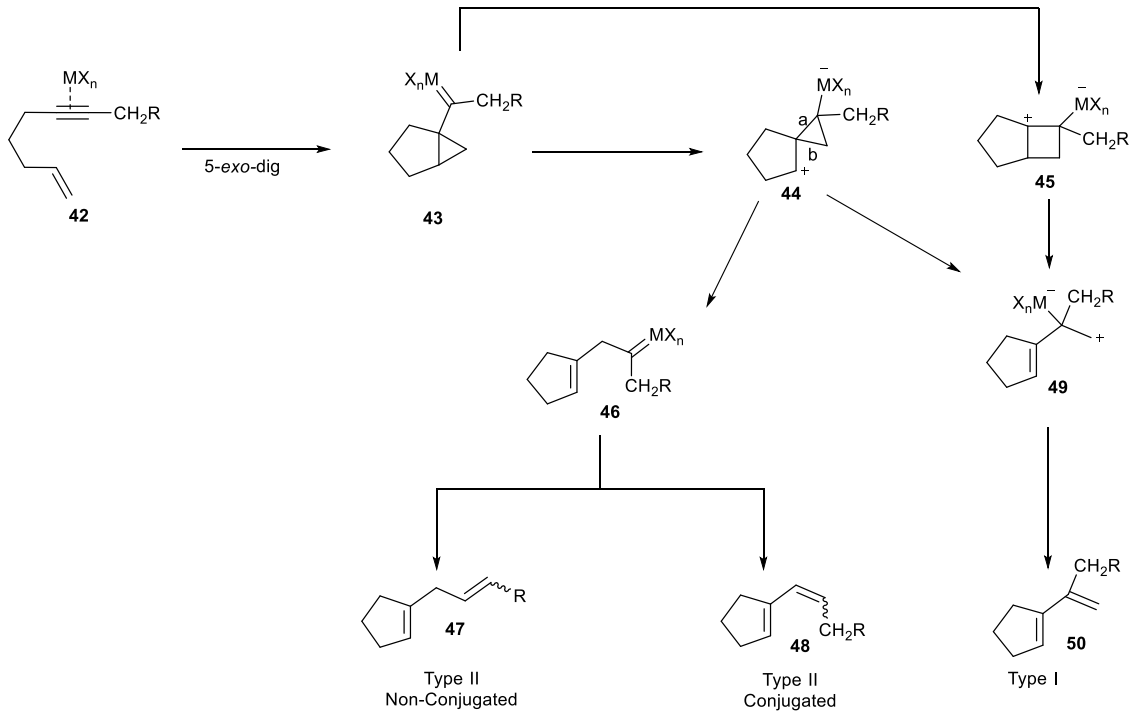
It is beyond the scope of this introduction to cover the wide and diverse reactions of allenes *via* gold(I)-catalysis. However, a brief introduction to intra- and intermolecular addition to allenols will be covered in Chapter 2. A brief introduction will also be given in Chapter 6 which will cover chirality transfer reactions of allenes.

1.5 Indium Catalysis

Initial investigations at the beginning of this PhD project began with Au(I) catalysis (Chapter 2). However, it was soon discovered that Au(I) was not the most effective catalyst for the dehydrative reaction of allenols. However, In(III) catalysed the reaction efficiently (Chapter 2). Therefore, a brief introduction to indium will be covered here.

Indium(III) salts and complexes are similar to gold in that they air stable and non-toxic [29] and are known to catalyse many different reactions including, but not limited to, Diels-Alder,[30] cycloisomerisation of 1,6-enynes,[31] hydroamination and hydroalkylation of alkynes,[32] and has applications in asymmetric catalysis.[33]

As with Au(I), $InCl_3$ is known to catalyse the cyclisation of enynes (Scheme 1.11). However, unlike Au(I) and many other catalysts which catalyse this reaction, $InCl_3$ produces the non-conjugated diene **47** rather than the conjugated diene **48** or **50**.[31]



Scheme 1.11: Cyclisation of enynes to give either type I or type II diene products

It was proposed that the mechanistic pathway starts with the activation of the alkyne to form complex **42**. This complex then reacts with the alkene part of the enyne substrate to form complex **43**. In type I cycloisomerisations, complex **43** can be transformed into the cyclobutane intermediate **45**. This intermediate then undergoes ring-opening and dissociates the catalyst to form the type I diene product **50**. In type II cycloisomerisation,

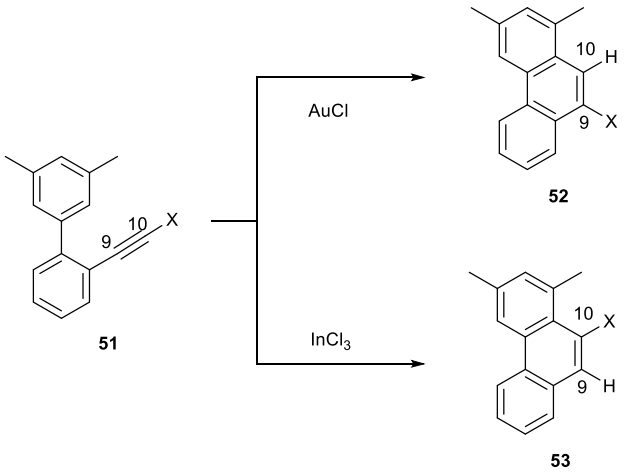
skeletal rearrangement of **43** gives spiro intermediate **44**. This can then undergo bond cleavage of *a* to form intermediate **46**. A subsequent hydrogen shift and dissociation of the catalyst produces a type II diene, either **47** (*via* non-conjugated [1,2]-H shift) or **48** (*via* conjugated [1,2]-H shift) depending on the R group on the alkyne region of the substrate.[31]

When internal alkyne substrates were used in conjunction with $InCl_3$ as a catalyst, only non-conjugated dienes were formed **47**. Zhuo *et al*. were interested in many aspects of this reaction including which factors determine the regioselectivity, why non-conjugated dienes are favoured and most importantly, what is the real catalytic species of the reaction?

Zhuo *et al*. computed the energy surface for both $InCl_3$ and $(InCl_3)_2$. However, both of these catalysts favoured the conjugated diene product suggesting that neither of these species is the active catalyst for the reaction. Instead, the group proposed that the catalytic species could be $InCl_2^+$ which is generated from the dissociation of 2 $InCl_3 \rightarrow InCl_2^+ + InCl_4^-$. Indeed, when the energy surface of the cycloisomerisation using $InCl_2^+$ as the catalytic species was calculated, only the non-conjugated diene was formed.[31]

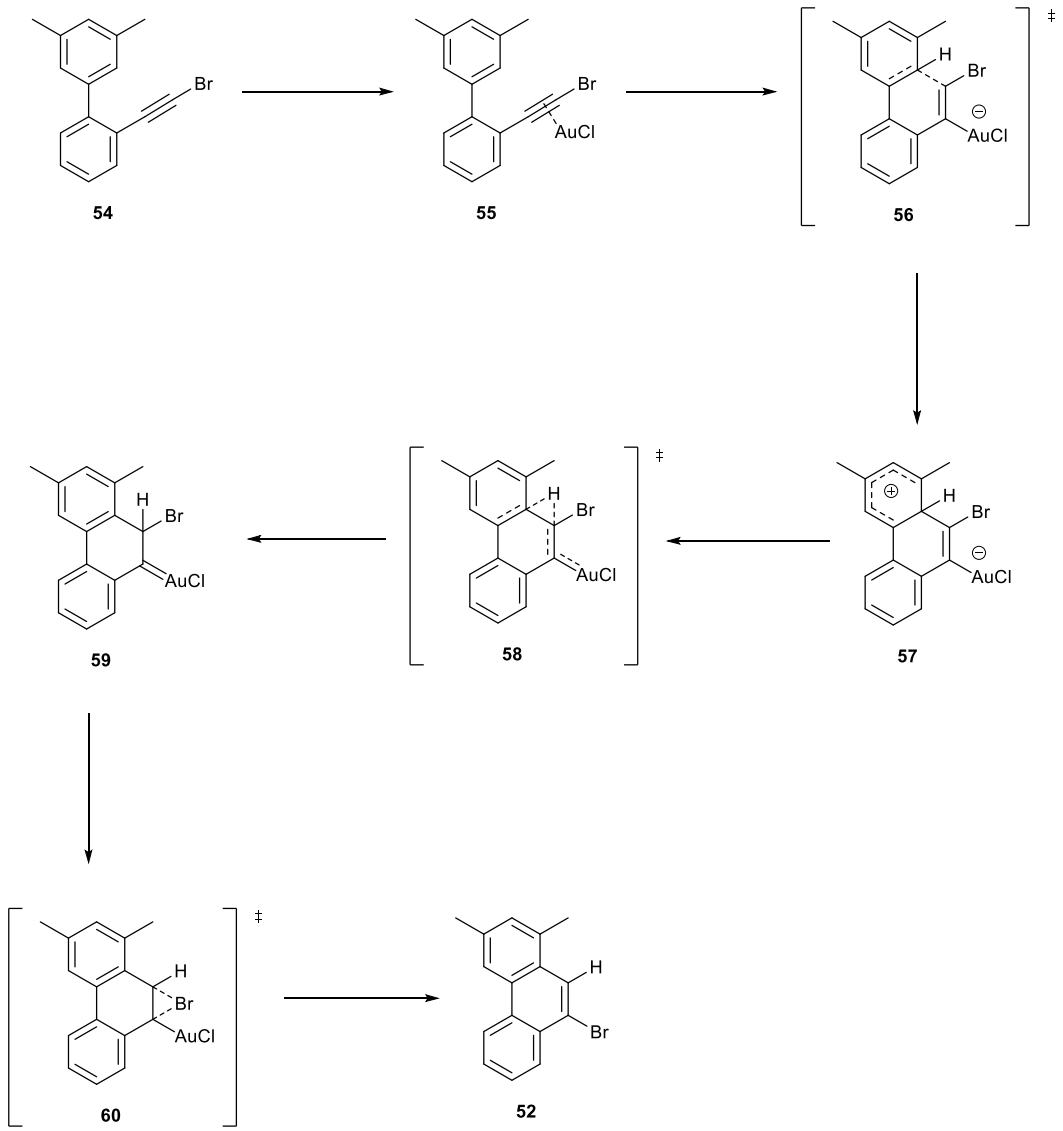
As with the cycloisomerisation of enynes there have also been several other studies which compare reactions under indium(III)- and Au(I)-catalysis. These studies found that In(III) and Au(I) usually produce different products from the same starting materials under similar reaction conditions.[32, 34]

In 2012, Huang *et al*. studied the mechanism of transition metal-catalysed hydroarylation of bromoalkynes; in particular the hydrogen *vs* bromine migration. Both AuCl and $InCl_3$ catalyse the reaction, however, whilst AuCl produces a 9-halophenanthrenes **52**, $InCl_3$ produces 10-halophenanthrenes **53** (Scheme 1.12).



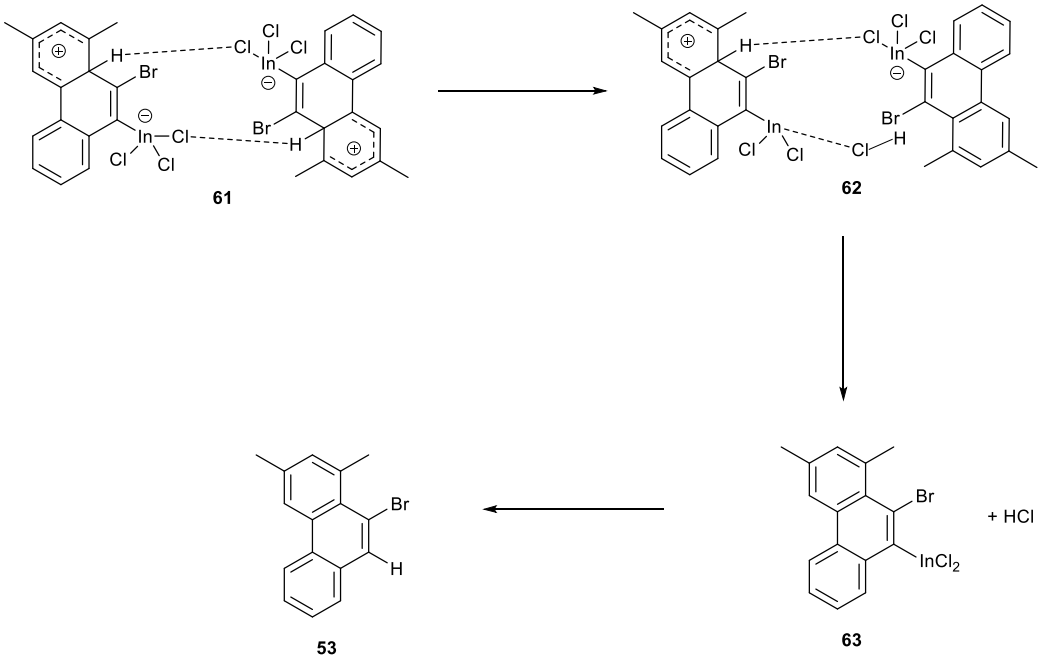
Scheme 1.12: Transition-metal-catalysed intramolecular hydroarylation reaction of haloalkynes

Computational studies revealed that although both catalysts favour the 6-*endo*-dig cyclisation, the formation of 9-bromo- and 10-bromo-phenanthranenes arises from differences in the H-migration pathways of the generated Wheland-type intermediates. In the case of AuCl, the 1,2-H/1,2-Br migration sequence of **51** leads to the 9-bromophenanthrene product **52** only (Scheme 1.13). First, AuCl co-ordinates to the alkyne to form complex **55** which then undergoes a Friedel-Crafts type reaction to produce wheland intermediate **57** *via* a 6-*endo*-dig cyclisation pathway. Next, a 1,2-H shift occurs *via* transition state **58** which leads irreversibly to the gold carbenoid **59**. Finally, a 1,2-Br shift occurs *via* transition state **60** to give the 9-halophenanthranene product **52** (Scheme 1.13).[34]



Scheme 1.13: AuCl reaction pathway

The group originally proposed the same mechanistic pathway for $InCl_3$ which also produced the 9-halophenanthrene **52**. However, this result was contradictory to the experimental evidence. Therefore, to account for the experimental observations the group considered alternative pathways to the 10-halophenanthrenes. One of the pathways considered was intramolecular H-migration with the assistance of the chloride ligand of $InCl_3$ (Scheme 1.14). In this mechanistic pathway complex **61** is formed by two hydrogen bonded intermediate **57** complexes. A proton is then abstracted by Cl to form the zwitterionic intermediate **62** which then dissociates to form two molecules of **63** and HCl. Finally, protodemetallation of complex **63** produces then 10-halophenanthranene **53** (Scheme 1.14).



Scheme 1.14: Mechanistic pathway for $InCl_3$

Since indium has been shown to catalyse many reactions which can also be catalysed by gold(I) but may, in some cases, produce different products, these two catalysts have been compared in Chapters 2 and 3.

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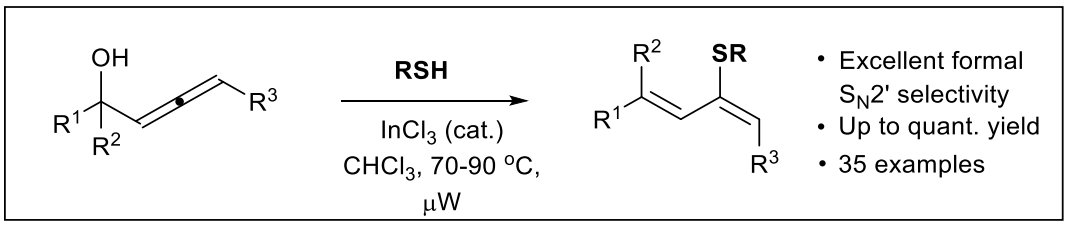
Chapter 2: Dehydrative Thiolation of Allenols – Indium vs. Gold Catalysis



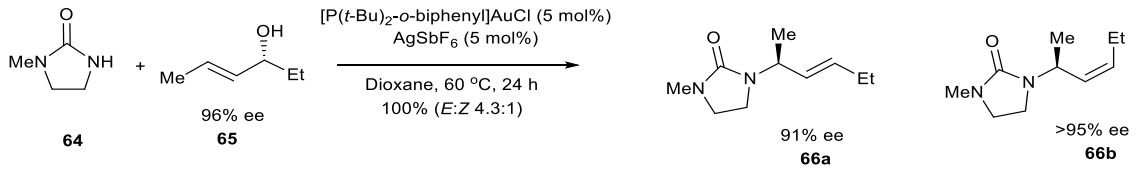
Acknowledgements

The author would like to thank Paul Young for the synthesis of substrate **86a** and for exploratory experiments at the beginning of this project.

2.1 Introduction

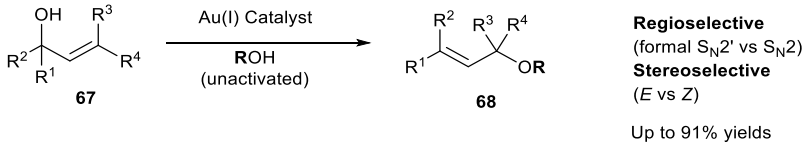
In recent years, gold-catalysis has become a widespread area of research due to gold's ability to act as a soft Lewis acid and activate carbon-carbon multiple bonds in particular alkenes, alkynes and allenes. In fact, many gold-catalysed reactions, unlike other transition metal-catalysed reactions, can be carried out without the need of dry solvents or an inert atmosphere.[1]

More recently, gold-catalysed, dehydrative reactions involving allylic alcohols have emerged as a mild and selective method for allylations. In 2010, Widenhoefer and co-workers developed a gold-catalysed amination reaction of allylic alcohols **65** with cyclic ureas **64** (Scheme 2.1). Although it was mainly a racemic study, there was one example with chirality transfer.[2]



Scheme 2.1: Gold catalysed amination reaction of allylic alcohols

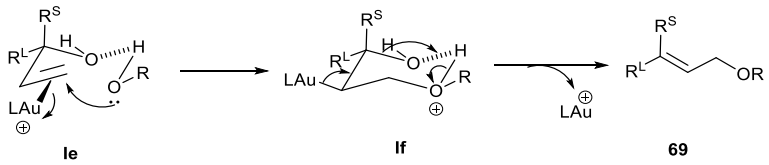
The Lee group have also recently investigated this area and have developed a gold-catalysed intermolecular etherification reaction of allylic alcohols (Scheme 2.2). This reaction is regioselective (formal S_N2' product **68**), mild, air-stable and additive free,[3] thus providing advantages compared to previously reported procedures using other metals and allylated substrates.[4]



Scheme 2.2: Gold catalysed intermolecular etherification reaction of allylic alcohols

Not only is the reaction practical: having no need for dry solvents or inert atmosphere, it also displays a wide substrate scope including unactivated primary, secondary and tertiary allylic alcohols and alcohol nucleophiles with good to excellent yields. As well as being regioselective and high yielding, the reaction was also stereoselective for the *E* isomer.

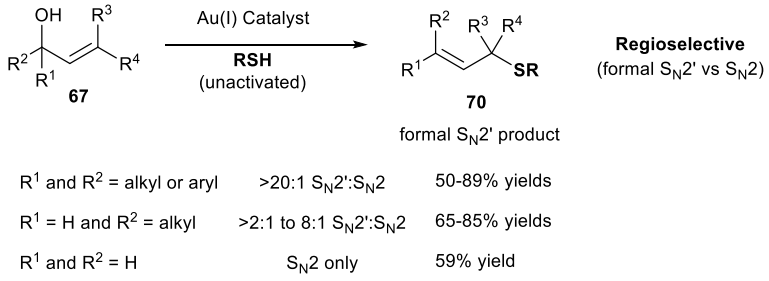
With stereoselectivity in mind the group proposed the following mechanism (Scheme 2.3).[3]



Scheme 2.3: Proposed mechanism for the gold catalysed etherification of allylic alcohols

The gold(I)-catalyst first activates the alkene of the allylic alcohol towards nucleophilic attack by an external alcohol nucleophile (**Ie**, Scheme 2.3). Demetallation and elimination of water (possibly aided by hydrogen bonding, **If**), would then follow to regenerate the catalyst and the desired product **69**. The good *E* stereoselectivity is thought to arise from the chair-like 6-membered ring transition state. To provide evidence for this, the group performed the reaction in neat isopropyl alcohol which would disrupt hydrogen bonding in **Ie** and **If**, and indeed observed a significant decrease in *E*/*Z* ratio.[3]

The Lee group then further developed this reaction by investigating thiols as nucleophiles to synthesise thioethers (Scheme 2.4). Organosulfur compounds are of particular importance in organic chemistry as they are present in many biological structures, including seven out of ten of the best selling drugs in the US in 2009.[5] However, using thiols as nucleophiles with transition metals can be problematic due to sulfur's ability to poison transition metals.[6] Despite the possibility that thiols may deactivate the gold catalyst, the group were able to develop a mild, selective and atom economical reaction with only water as a by-product (Scheme 2.4).[7]

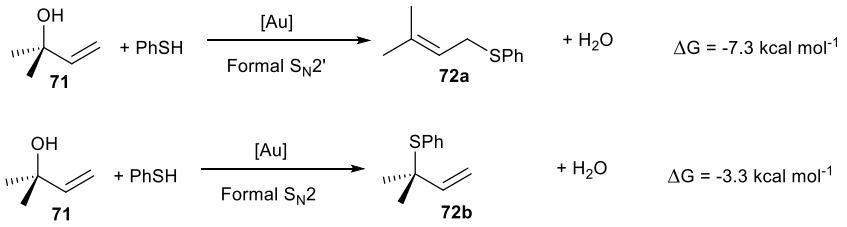


Scheme 2.4: Mild, gold-catalysed thioetherification reaction.

The reaction has a wide nucleophile scope including electron rich and electron deficient aryl thiols with yields >60%, and alkyl thiols also performing well. The reaction also has

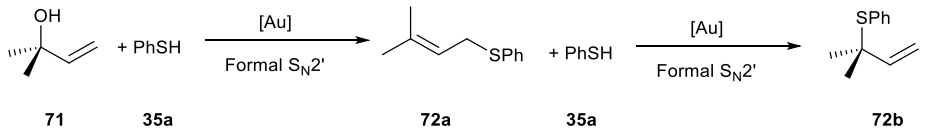
a wide substrate scope with both tertiary allylic alcohols reacting selectively to produce the formal S_N2' product **70** in good to excellent yields. Although secondary allylic alcohols also reacted well, when R^1 = H and R^2 = alkyl group then S_N2':S_N2 ratio decreases. Furthermore, when R^1 and R^2 = H only the S_N2 product was observed.[7]

In order to account for the regioselectivity observed during the experimental work, computational studies were carried out. It was calculated that the excellent regioselectivity observed during the experimental work was due to the thermodynamic stability of the products. Calculations show that the formal S_N2' product **72a** is 4 kcal mol^{-1} more stable than the formal S_N2 product **72b** as shown in Scheme 2.5.



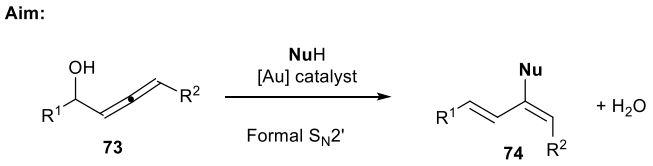
Scheme 2.5: Computed thermodynamic stability of products

Computational studies suggested that if any of the formal S_N2 products were observed experimentally, it would be the result of two formal S_N2' steps, with this route being kinetically favoured over a direct S_N2 reaction (Scheme 2.6).[7]



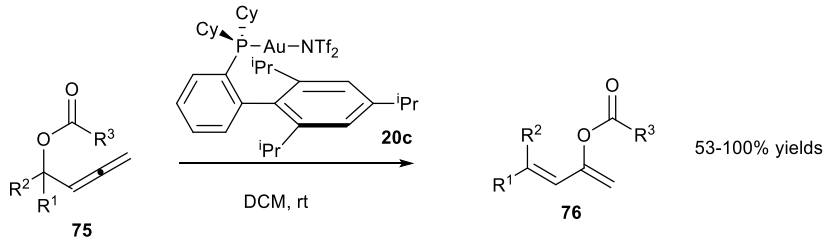
Scheme 2.6: Formation of the formal S_N2 product by two formal S_N2' steps

To summarise, gold-catalysed etherifications and thioetherifications with allylic alcohols are highly regioselective for the formal S_N2' reaction. Therefore, at the outset of this project, our aim was to apply this intermolecular dehydrative method to *allenols* to produce functionalised dienes **74** (Scheme 2.7).



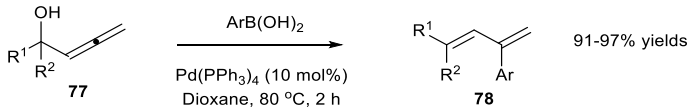
Scheme 2.7: Current aim

At the start of the project, there were no reports in the literature of intermolecular reactions with allenols under Au(I)-catalysis to form 1,3-dienes. However, Gagosz and co-workers developed a gold(I)-catalysed isomerisation reaction of allenyl carbinol esters **75** to form functionalised 1,3-butadien-2-ol esters **76** (Scheme 2.8). This reaction produced excellent yields of 1,3-dienes (53-100%) but the *E*/*Z* ratio was often poor with several examples <10:1 *E*/*Z*.[8]



Scheme 2.8: Au(I) catalysed isomerisation of allenyl carbinol esters

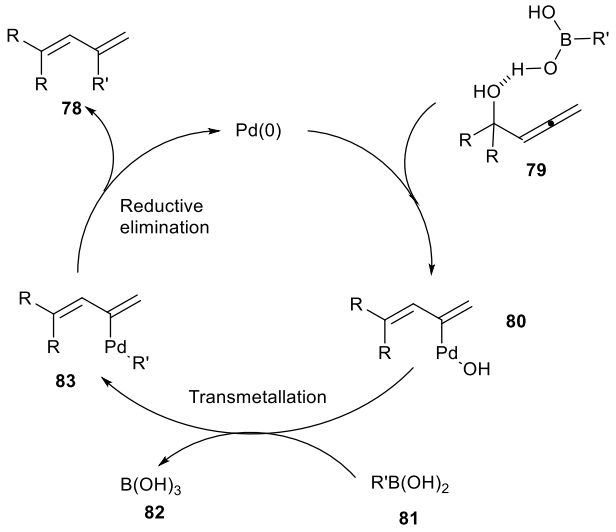
Although there are no gold-catalysed intermolecular reactions of allenols reported in the literature, there have been several examples of intermolecular reactions with palladium. Yoshida *et al.* developed a Pd-catalysed coupling reaction of allenols **77** with aryl- and alkenyl boronic acids to form 1,3-dienes **78** (Scheme 2.9).[9]



Scheme 2.9: Pd-catalysed coupling reaction of allenols with boronic acids

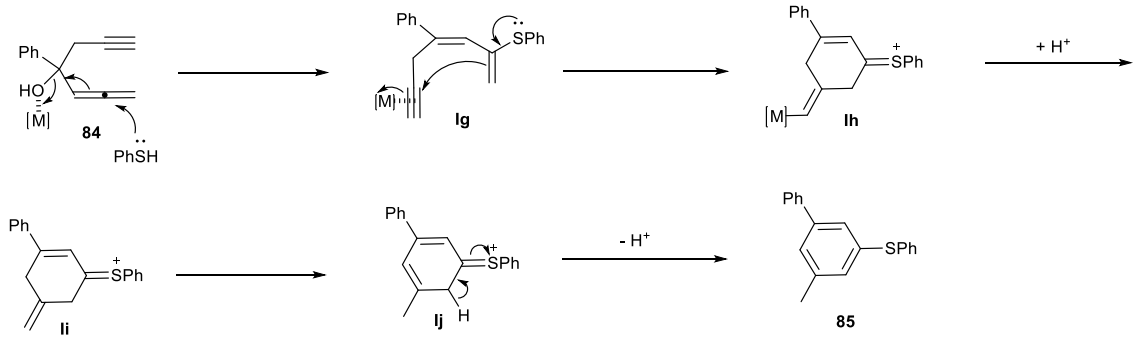
This method provided excellent yields of the desired 1,3-diene products **78**. However, the *E/Z* ratio was poor in most cases, 1.5:1 to >20:1. It is thought that the Pd(0) attacks in an S_N2' fashion at the allene quaternary centre to form an allylpalladium hydroxide species **80** (Scheme 2.10). This species transmetallates with the boronic acid, followed by a reductive elimination to release the catalyst and the 1,3-diene **78** (Scheme 2.10).[9] There

have been several papers relating to the synthesis of dienes using palladium catalysis, including the formation of 2-halo-1,3-dienes,[10] and 2-furanone substituted 1,3-dienes.[11]



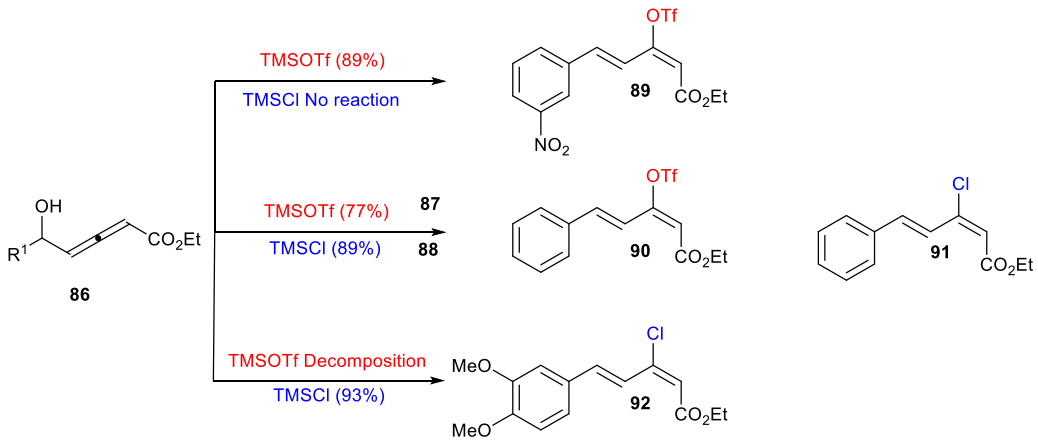
Scheme 2.10: Proposed mechanism for Pd-catalysed coupling reaction of allenols with boronic acids

Dienes are also thought to be intermediates in the InI_3 or ZnI_2 catalysed reaction of hydroxylated 1,5-allenynes with thiols to produce toluene derivatives (Scheme 2.11). It was proposed by Ma *et al*. that the metal first acts as a Lewis acid to activate the hydroxyl group, followed by an attack of the thiophenol on the central carbon of allene **84**. Elimination of the hydroxyl group then leads to the 1,3-diene intermediate **Ig** (not isolated). The enol thioester functions as a strong nucleophile to attack the activated triple bond to give intermediate **Ih** followed by protodemetallation to produce intermediate **Ii**. The final arene product **85** is then formed by a rearrangement and deprotonation of intermediate **Ii**.[12]



Scheme 2.11: Proposed mechanism by Ma *et al.*

There have also been several reports on the formation of 1,3-dienes without the use of a transition metal catalyst. In 2013, Sabbasani *et al.* reported a metal-free rearrangement reaction of allenols **86** with TMSOTf and TMSCl to produce 1,3-dienes **89**–**92** in excellent yields (Scheme 2.12).[13]



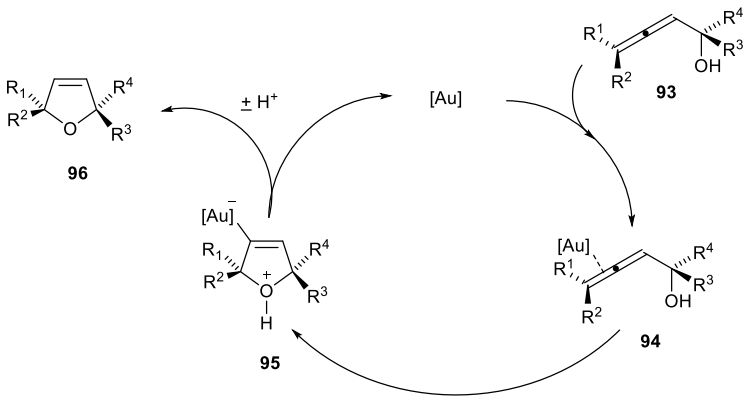
Scheme 2.12: Rearrangement of allenols

It was observed from this reaction that subtle electronic effects within the aryl ring played an important role in determining the rate of reaction and in the formation of vinyl triflates and vinyl chlorides. Allenols containing electron-deficient aryls reacted with TMSOTf efficiently to produce the desired product, but under the same conditions TMSCl failed to react. In the case of allenols with electron-rich aryls, only TMSCl reacted efficiently whereas the use of TMSOTf resulted in decomposition.[13] Using similar allenols to that of Sabbasani *et al.*, Cheng and co-workers developed a base-catalysed reaction to synthesise 2-amino-1,3-dienes. However, this reaction required high temperatures and anhydrous conditions.[14]

Although there were no examples of gold-catalysed intermolecular nucleophilic additions to allenols to form dienes during the start of our project, there were many examples of intramolecular cyclisations of allenols under gold catalysis. It is therefore possible that the lack of the former may be due to the propensity of allenols to react intramolecularly under gold catalysis.

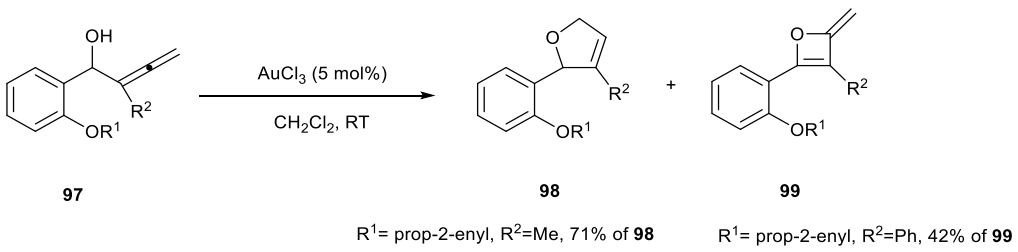
The first intramolecular cyclisation of an allene in the presence of gold was reported by Hashmi and co-workers, involving the formation of a substituted furan from an α-allenyl ketone.[15] In subsequent years, this reaction was developed by Krause and co-workers to include the cyclisation of α-hydroxyallenes **93** in the presence of a gold(III)-catalyst to

form 2,5-dihydrofurans **96** in good to excellent yields of 77-95% (Scheme 2.13).[16] This chemistry can also be applied to β-hydroxyallenes to yield dihydropyrans with yields ranging from 50-84%.[17]



Scheme 2.13: General mechanism for the cyclisation of allenols

Cyclisation reactions of allenols usually favour 5-*endo*-trig cyclisation reactions (Scheme 2.13). However, in 2011 this type of reaction was further explored by Fernández and co-workers and it was subsequently shown that formation of 4-membered rings are also possible and that the reactions proceeds through a 4-*exo*-dig cyclisation reaction (Scheme 2.14). Fernández and co-workers observed that by modulating the relative stability of the η^2 complexes generated by π-coordination of the metal to the C=C bonds during the reaction, they were able to alter the selectivity (Scheme 2.14).[18]



Scheme 2.14: Oxycyclisation reaction of α-allenols in the presence of a gold catalyst

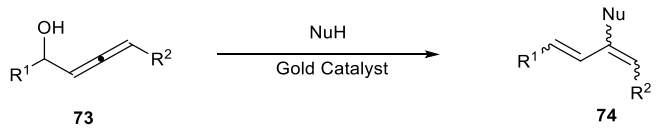
At room temperature and in the presence of a gold(III)-catalyst, when R^2 is a methyl group and R^1 is prop-2-enyl, a 71% yield of the 5-membered ring **98** was obtained (Scheme 2.14). However, by keeping R^1 as prop-2-enyl but substituting R^2 with a phenyl ring at room temperature, the group observed 42% of the 4-membered ring only. When the reaction was carried out at 40 °C, the 4-membered ring was the sole or major product. This observation suggests that the 4-membered ring is thermodynamically favoured,

whereas the 5-membered ring is kinetically favoured. This was later confirmed by computational studies.[18]

In summary, the Lee group have recently developed an intermolecular gold(I)-catalysed reaction of allylic alcohols with both alcohol (Scheme 2.2) and thiol (Scheme 2.4) nucleophiles. This reaction is highly regioselective, where a formal S_N2' reaction is favoured over the formal S_N2. The aim of this project was to expand the substrate scope to allenols **73** for the formation of 1,3-dienes **74**. Although there have been several papers of intermolecular transition metal-catalysed additions to allenols, no such papers have been published using Au(I) as a catalyst. This is presumably due to the well documented area of the intramolecular cyclisation of allenols under gold-catalysis.

2.2 Project Aim

The aim of this project is to determine whether allenols (**73**) can undergo a gold-catalysed intermolecular formal S_N2' reaction with a nucleophile to produce functionalised 1,3-dienes (**74**), which are useful building blocks in organic synthesis. For example, dienes can feed into a wide range of further reactions such as 1,4-cycloadditions (Diels-Alder reactions). Such a reaction, if successful, would be unprecedented as allenols usually undergo *intra*molecular cyclisation reactions in the presence of gold.

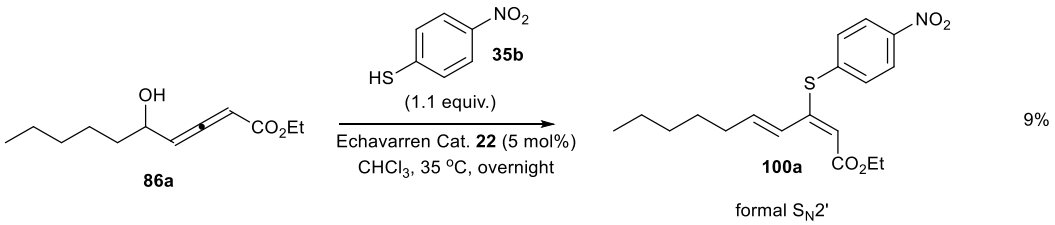


73 **74**

Scheme 2.15: Proposed intermolecular formal S_N2' reaction of an allenol in the presence of a gold catalyst and a nucleophile

If successful, the reaction will be optimised and substrate as well as nucleophile screens will be carried out.

Early exploratory studies carried out by Paul Young within the Lee group showed a promising 9% yield of the formal S_N2' product **100a** when 4-nitrothiophenol is used as a nucleophile (**35b**, Scheme 2.16).



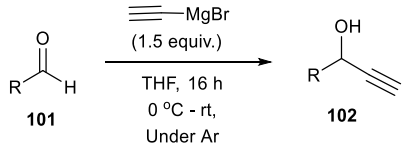
Scheme 2.16: Initial reaction carried out by Paul Young

2.3 Results and discussion

2.3.1 Substrate synthesis

The project commenced with the synthesis of various propargylic alcohols to form allenols to be investigated as substrates. Known and unknown compounds were synthesised by following or adapting known literature procedures.

Propargylic alcohols are easily synthesised in a one-step synthesis by reacting the corresponding aldehyde with ethynlmagnsium bromide (Scheme 2.17).



Scheme 2.17: Synthesis of propargylic alcohols

Allenols are readily available in two steps or less, and for this reaction it was decided that ethyl allenoates (Figure 2.1, **86**) would be better suited for initial test reactions. It was hoped that substituting an ester group at the R^2 position would decrease the electron density of the C=C bond at position C3-C4. This should encourage the gold(I) catalyst, which is electrophilic, to coordinate to the C=C bond at position C2-C3 and thus prevent the unwanted intramolecular cyclisation (shown in Section 2.1).

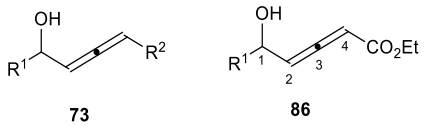
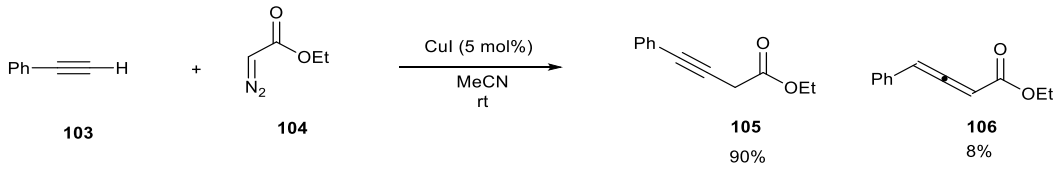


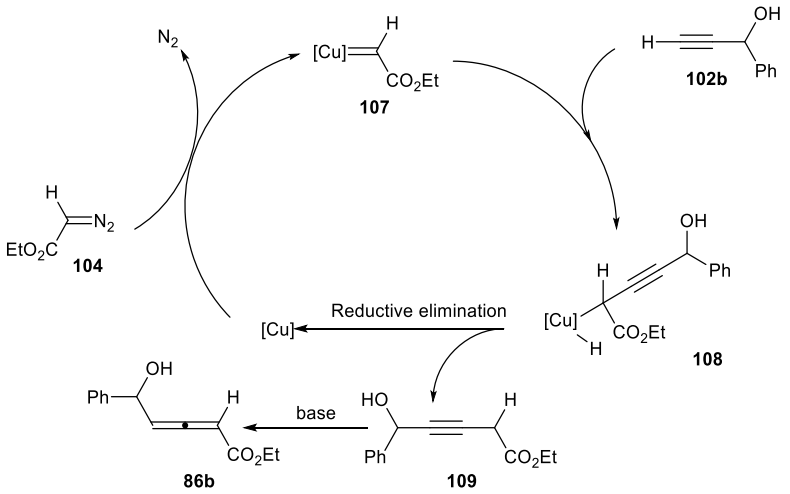
Figure 2.1: Allenols and allenoates

Many of the substrates used in these reactions have been synthesised by Sabbasani *et al.*[13] who adapted and optimised the work carried out by Fu and co-workers for the synthesis of alkynoates.[19] Fu and co-workers initially observed both the alkynoate **105** and the allenoate **106** as impurities when they reacted a propargylic alcohol with ethyl diazoacetate **104** (EDA) in the presence of CuI (catalyst) in acetonitrile (Scheme 2.18). The choice of solvent was critical as other solvents including ^{i}PrOH, THF, dioxane, acetone or $CHCl_3$ led to significantly lower yields.[19]



Scheme 2.18: Synthesis of alkynoates and allenoates by Fu *et al.*

Sabbasani *et al.* adapted this procedure by adding a stoichiometric amount of triethylamine, which effectively isomerises the alkynoate **105** to the corresponding allenoate **106** in 3 hours with yields >70%.[13] Although Sabbasani *et al*. do not propose a plausible mechanism, it is thought to proceed through a similar mechanism described by Hassink *et al.* for the formation of 2,4-disubstituted allenoates **86b** from α-diazoesters **104** (Scheme 2.19).[20]



Scheme 2.19: Possible catalytic cycle for the formation of allenoates

Copper reacts with the α-diazoester **104** to give a carbenoid **107** (Scheme 2.19), which then reacts with the terminal alkyne **102b** possibly proceeding *via* intermediate **108**, which can then undergo a reductive elimination to regenerate the catalyst and the alkynoate **109**. In the presence of a base, the alkynoate **109** is isomerised to the corresponding allenoate **86b**.[20]

However, when this procedure was repeated, we found that our yields were significantly poorer than that achieved by Sabbasani *et al*. (34% *vs* 90% **86b**) and some substrates failed to react at all. To improve the yield, distilled triethylamine was used, but only slightly improved yields were obtained. To further optimise the procedure, the method by Hu *et al.* was adopted. The propargylic alcohol, EDA and CuI were stirred in MeCN for 12 hours under Ar to give a mixture of allenoate and alkynoate and then later converted

into the allenoate by stirring in Et_3N for 1.5 hours as a separate step (*vs* Sabbasani's procedure, where the NEt_3 is *in situ*). This procedure gave excellent yields of the desired allenoates **86**. A summary of these ethyl allenoates is given in Table 2.1.

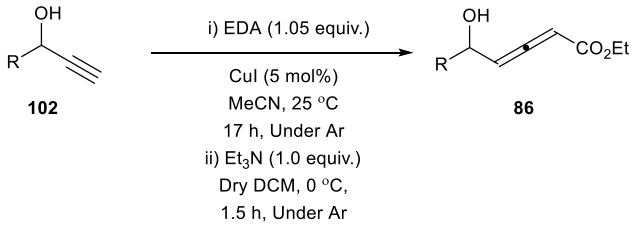
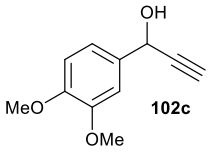
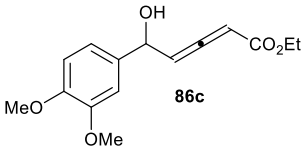
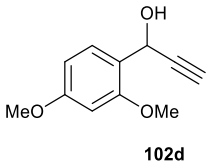
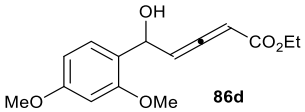
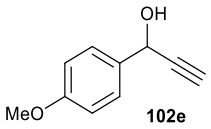
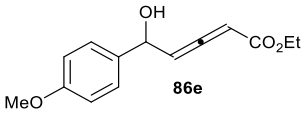
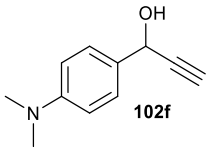
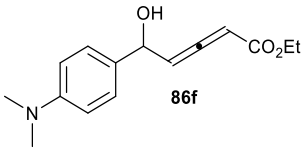
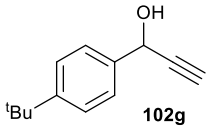
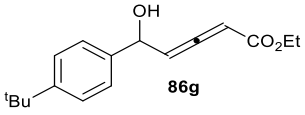
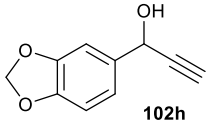
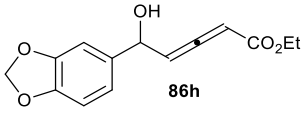
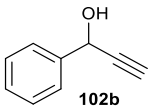
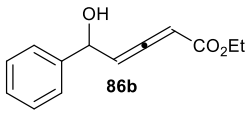
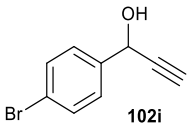
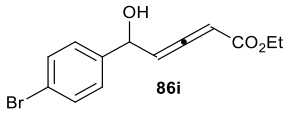
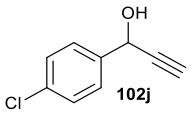
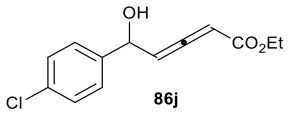
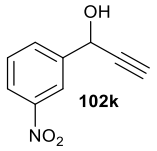
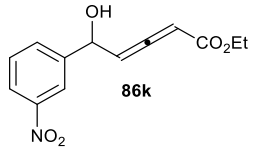
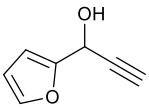
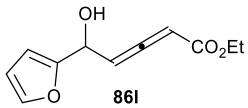
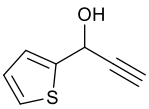
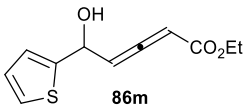
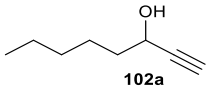
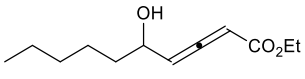
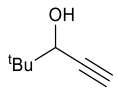
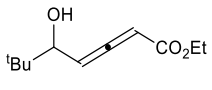
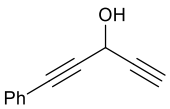
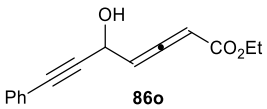
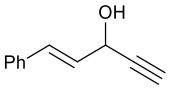
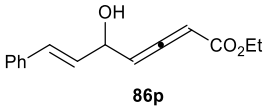
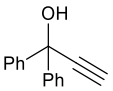
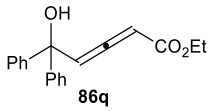


Table 2.1: Summary of Substrates

Entry	Substrate	Product	Yield (%)
1			90[a]
2			89
3			78
4			39[a]
5			63
6			63
7			93

8	 **102i**	 **86i**	60[a]
9	 **102j**	 **86j**	95[a]
10	 **102k**	 **86k**	6
11	 **102l**	 **86l**	71[a]
12	 **102m**	 **86m**	16
13	 **102a**	 **86a**	18[b]
14	 **102n**	 **86n**	72
15	 **102o**	 **86o**	82[a]
16	 **102p**	 **86p**	84[a]
17	 **102q**	 **86q**	97

[a] Et_3N not required, full conversion to allenoate after step i). [b] One pot procedure (with 1 equiv. Et_3N present) was used.

Products **73b-73q**, allenols without an ester substituent, were synthesised *via* a different procedure developed Kuang *et al*. (Table 2.2, entries 1-5).[21]

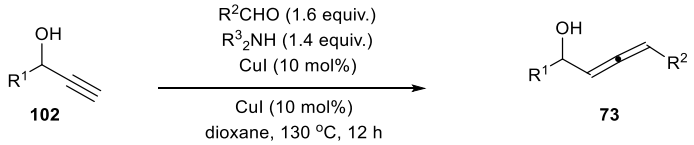
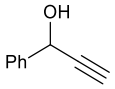
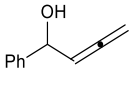
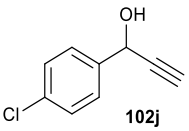
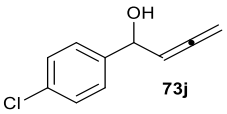
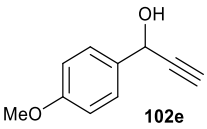
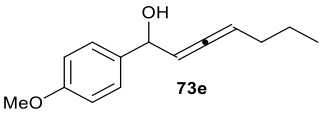
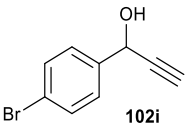
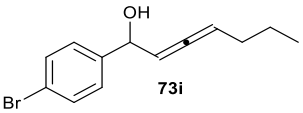
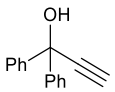
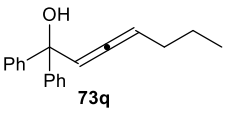
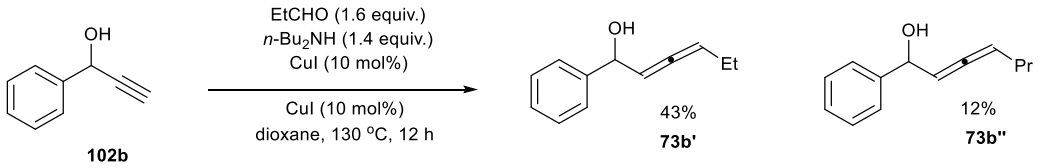


Table 2.2: Summary of allenol substrates without ester substituent

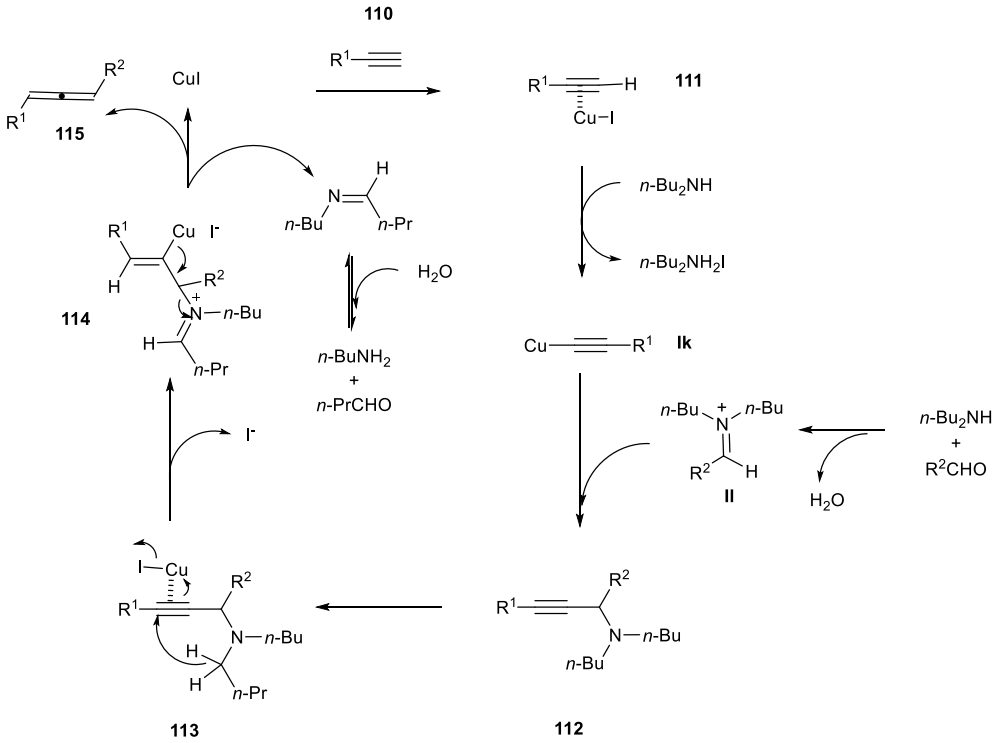
Entry	Substrate	Product	Yield (%)
1	 **102b**	 **73b**	76
2	 **102j**	 **73j**	29
3	 **102e**	 **73e**	29
4	 **102i**	 **73i**	62
5	 **102q**	 **73q**	19

A copper catalyst and a base were still required for these reactions. However, the EDA was replaced with an aldehyde. For terminal allenols (entries 1 and 2) paraformaldehyde is used, whilst for the reactions shown in entries 3-5 the corresponding aldehyde is butanal. For these particular reactions Kuang *et al.* discovered that the choice of base in the reaction was critical; if the dialkylamine used did not match the aldehyde, a mixture of allenes was produced (Scheme 2.20).[21]



Scheme 2.20: Effect of incorrect base with aldehyde

Therefore, for products **73e**-**73q**, di(*n*-butyl)amine was used. Although the reactants are slightly different (EDA *vs* aldehyde), the mechanism for both reactions are similar in that the copper intermediates with the alkyne are still formed, but the base takes on a larger role than simply isomerising the alkyne to the allene as shown in Scheme 2.21.

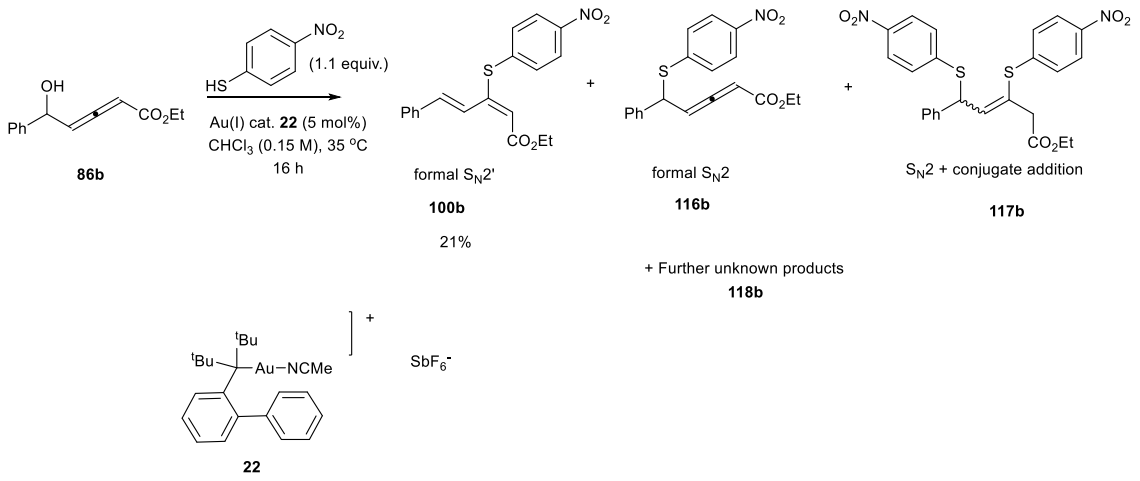


Scheme 2.21: Proposed mechanism for the formation of allenes from terminal alkynes by Ma and co-workers[21]

The reaction of the CuI with the terminal alkyne in the presence of a base would form the alkynynl copper intermediate **Ik**, which would then react with the *in situ* generated iminonium intermediate **Il** to yield propargylic amine **112**. An intramolecular hydride transfer followed by elimination would then yield the allene product **115** regenerating the CuI catalyst.[21]

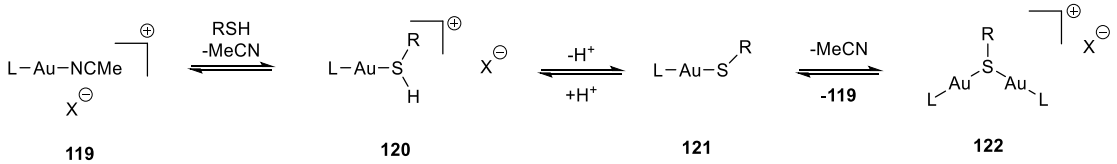
2.3.2 Dehydrative Thiolation of Allenols Optimisation

The initial reaction investigated involved reacting allenol **86b** with 4-nitrothiophenol in the presence of gold(I)-catalyst **22** (Scheme 2.22). 4-Nitrothiophenol successfully acted as a nucleophile for this reaction, despite thiol's ability to reduce the activity of the gold catalyst.[22]



Scheme 2.22: Initial reaction

Recent work done by the Lee group suggests that the Echavarren catalyst **22** is more tolerant of sulfur nucleophiles than other gold(I)-catalysts, such as PPh_3AuNTf_2 developed by Gasgosz.[23] When gold(I) and sulfur nucleophiles are both present, the gold catalyst is deactivated by the formation of a digold species with a bridging thiolate complex **122** which are stable for greater than 3 months (Scheme 2.23). The digold complex **122** and the active catalyst **119** are in equilibrium, but in order to have a sufficient quantity of the active catalyst present, residual H^+ *in situ* is required.[22]



Scheme 2.23: Plausible mechanism for the deactivation of gold(I) by thiols

Initial gold-catalysed reactions showed poor selectivity to yield several different products (Scheme 2.22). The desired formal S_N2' product **100b** was obtained in a 21% yield, however, three different side products were also produced. Side product **116b** is produced through the formal S_N2 pathway. Side product **117b** is presumably formed *via* the formal S_N2 pathway followed by conjugate addition of a second thiol nucleophile onto **116b**.

The final side products **118b** are unidentified but may have arisen due to further reaction of the products with gold – see page 53 for details. Since the initial reaction promisingly produced desired product **100b**, attempts were made to optimise the reaction by performing temperature, solvent and concentration screens.

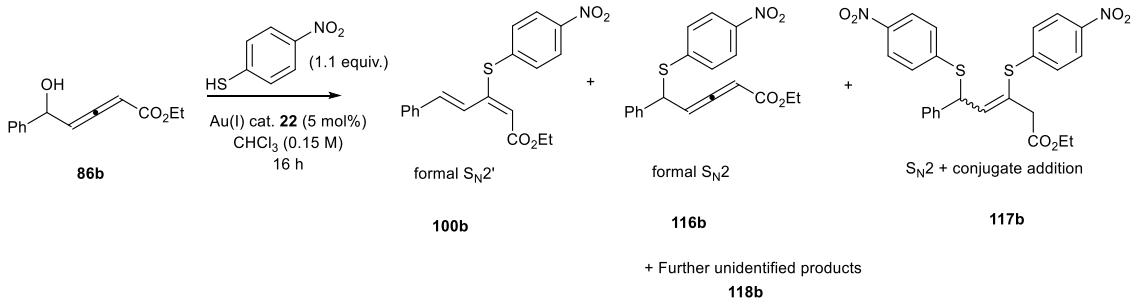


Table 2.3: Temperature Screen

Entry	Temp. (°C)	Yield formal S_N2' (100b)
1	rt	Complex mixture
2	35	21%[a]
3	50	32%[a]

[a]isolated yields.

Increasing the temperature from ambient to 50 °C, increased the yield and reduced the number of side products present in the reaction mixture (Table 2.3). However, the three major products were observed at all three temperatures but ratios could not be determined due to the complex nature of the reaction mixture. Next, a solvent screen was carried out (Table 2.4).

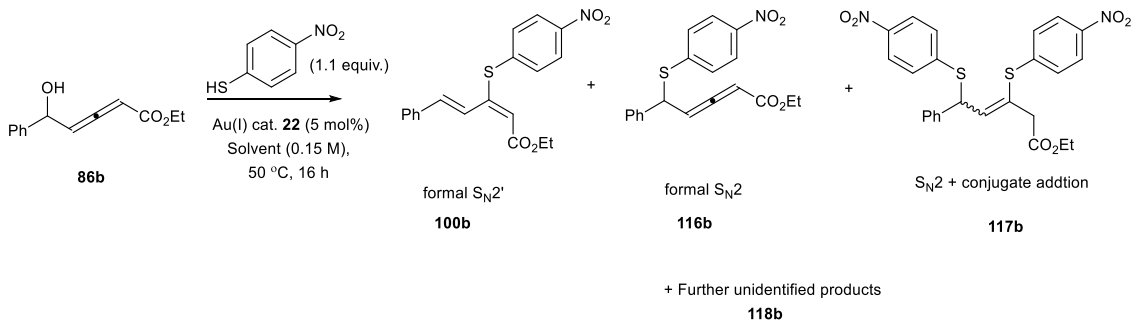


Table 2.4: Solvent Screen

Entry	**Solvent**	**S_N2': S_N2 100b:116b**	**117b**	**118b**	**Yield S_N2' (100b)**
1	Toluene	Observed 1:2	Observed	Observed	Complex mixture
2	Dioxane	-	-	-	Complex mixture
3	DCE	-	-	-	Complex mixture
4	$CHCl_3$	Observed[a]	Observed[a]	Observed[a]	32%[b]

[a] Observed in ^1H NMR of crude but ratios could not be determined accurately. [b] Isolated yield

It was found that $CHCl_3$ is the best solvent for the reaction (entry 4). Although toluene produces the desired formal S_N2' product **100b**, the reaction mixture is complex and the products could not be separated (entry 1). Neither dioxane or DCE, gave the formal S_N2' product **100b**, but the starting material was consumed to form a complex mixture of products (entries 2 and 3). The concentration of the reaction was investigated next (Table 2.5).

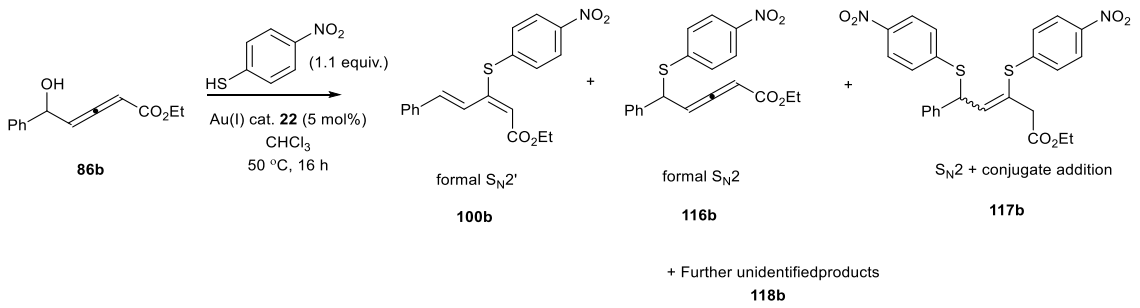


Table 2.5: Concentration Screen

Entry	Conc. (M)	100b:116b:117b	118b	Yield 100b
1	0.08	1:0.6:0.8	-	8%[a]
2	0.10	1:0.8:0.7	-	36%[a]
3	0.15	Observed[b]	trace	32%[a]
4	0.34	1:0:1	-	20%[a]

[a]Isolated yields. [b]Observed in ^{1}H NMR of crude material but ratios could not be determined accurately.

By decreasing the concentration from 0.34 M to 0.10 M, a 16% increase in the formal S_N2' product **100b** was observed (entries 2 and 4).

In an attempt to optimise the reaction further, conditions at higher temperatures were investigated using a microwave reactor. The use of sealed microwave tubes as a reaction vessel allows the reaction to be heated safely above its boiling point of the solvent in the microwave reactor.

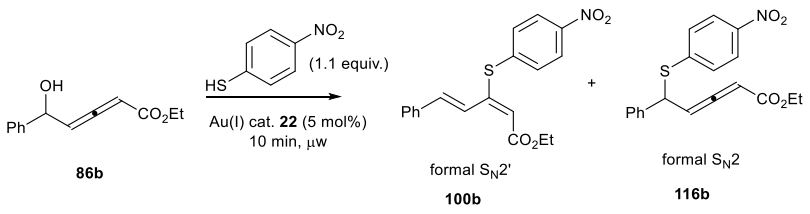


Table 2.6: Microwave conditions screen

Entry	Solvent	Conc. (M)	Temp (°C)	100b:116b	Yield 100b
1	$CHCl_3$	0.10	50	1:1.4	25%[a]
2	$CHCl_3$	0.10	60	1:1.6	27%[a]
3	$CHCl_3$	0.10	70	1:1	21%[a]
4	$CHCl_3$	0.10	80	1:1.1	31%[a]
5	Toluene	0.10	70	1:0.7	11%[b]
6	Dioxane	0.10	70	-	-
7	DCE	0.10	70	1:1	20%[b]
8	$CHCl_3$	0.05	70	1:0.7	25%[b]
9	$CHCl_3$	0.15	70	1:0.9	25%[b]

[a]Isolated yield. [b]Yield obtained by ^{1}H NMR analysis using dimethylsulfone as the internal standard. [c]**117b** and **118b** not observed in these reactions.

By heating the reaction, reaction times were decreased from 16 h to 10 min. This reduces the probability of the formal S_N2' product **100b** reacting further to produce unknown compound **118b**. Furthermore, side product **117b** was not observed. Using the microwave gave an additional advantage in that solvents could be superheated. It was shown that 70 °C was the optimum temperature for a cleaner reaction with less of the unwanted formal S_N2 product **116b** being formed (entry 3). This improved optimisation resulted in only two major products, the formal S_N2' **100b** and the formal S_N2 **116b**, instead of three as shown previously. It should be noted that the formal S_N2 product **116b** is unstable and decomposes in less than one month. It should also be noted that, in the experiments summarised in Table 2.6, the thiol and the Au(I) catalyst **22** were mixed before the allenol was added. This appeared to stop the formation of the conjugate addition product **117b**.

In summary, $CHCl_3$ is the most effective solvent for this reaction under microwave conditions and the optimum temperature is 70 °C. These conditions appear to lower the amount of the unwanted formal S_N2 product **116b** being formed, however, it is still

present even at these temperatures in a 1:1 ratio. Interestingly, at 35 °C more side products are observed.

All of the reactions were carried out with only 1.1 equivalents of the thiol nucleophile. In an attempt to improve the yield, the reaction was also carried out with 3 equivalents of thiol. However, this completely deactivated the catalyst and as a result none of the desired product was formed.

Different Au(I)-catalysts and counterions were investigated next in order to establish whether this would affect the **100b**:**116b** product ratio. No Au(I)-catalyst was able to effectively catalyse the reaction as effectively as the Echavarren catalyst **22** (Table 2.7) and altering the counterion did not improve the yield or the ratio of formal S_N2' **100b**:S_N2 **116b** (Table 2.7).

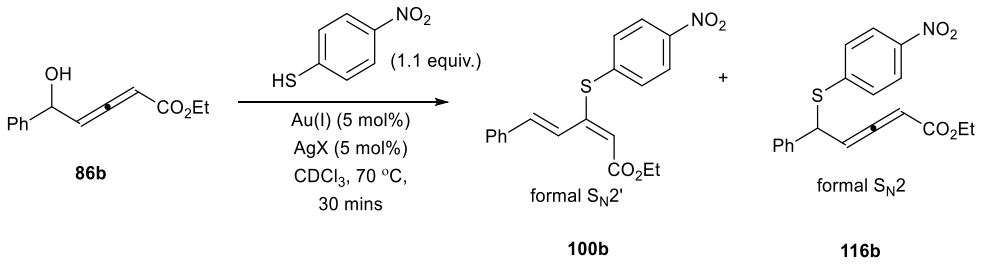
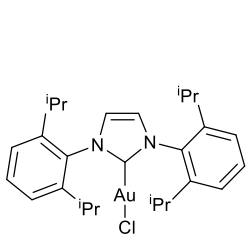


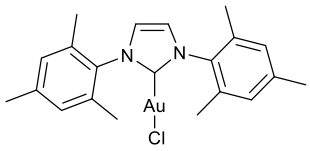
Table 2.7: Au(I) and counterion screen

Entry	Au(I)	Counterion AgX	Ratio 100b:116b	Yield S_N2' (%)
1	(IPr)AuCl	$AgSbF_6$	1:1.7	19[a]
2	PPh_3AuCl	$AgSbF_6$	1:2.5	10[a]
3	(IMes)AuCl	$AgSbF_6$	1:1.6	N/A[b]
4	**123**	$AgSbF_6$	1:1.2	15[a]
5[c]	(IPr)AuCl	$AgClO_4$	-	-
6	(IPr)AuCl	$AgBF_4$	1:1.4	16[a]
7[c]	(IPr)AuCl	$AgPF_6$	-	-
8[c]	(IPr)AuCl	AgOTf	-	-
9[c]	(IPr)AuCl	AgOTs	-	-

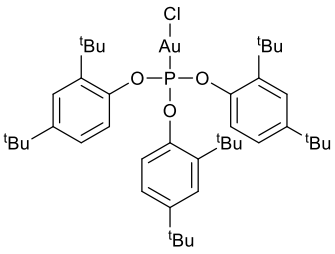
[a] Yield obtained by ^1H NMR analysis using dimethyl sulfone as a standard, [b] Still contained starting material, [c] Only starting material recovered.



25
(IPr)AuCl



26
(IMes)AuCl



123
$C_{42}H_{63}AuClO_3P$

Since the use of gold catalysts does not appear to be effective for this reaction, a Lewis acid screen was carried out (Table 2.8).

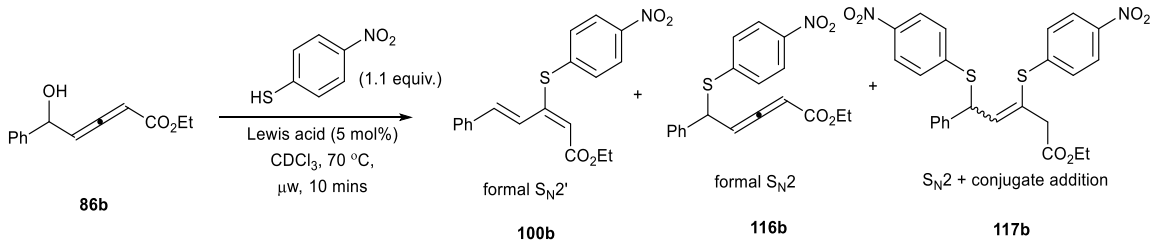


Table 2.8**:** Lewis Acid Screen

Entry	Lewis Acid	**100b**:**116b**:**117b**[a]	Yield **100b** (%)	Yield **116b** (%)
1	Au(I) cat. **22**	1:1:0	25[b]	30[b]
2	PPh_3AuNTf_2	1:1:5	ND	ND
3[d]	$NaAuCl_4 \cdot 2H_2O$	1:0:0	5[c]	-
4	Au(III) cat.	No reaction	-	-
5[b]	**$InCl_3$**	**10:0:1**	**47**[b]	**-**
6	InI_3	5:0:1	31[b]	-
7	$In(OTf)_3$	3:0:2	44[b]	-
8[d]	$Yb(OTf)_3$	1:0:1	10[c]	-
9[d]	$Sc(OTf)_3$	1:1:0	8[c]	8[c]
10[d]	$Ga(OTf)_3$	5:0:1	32[c]	
11	$FeCl_3$	Complex mixture	-	-
12	ZnI_2	1:0:2	10[b]	-
13	$AgSbF_6$	1:1:0	7[b]	
14	$PtCl_2$	No reaction	-	-

[a]Determined using ^{1}H NMR analysis of the crude reaction. [b]Isolated yields. [c]Yield determined using ^{1}H NMR analysis with dimethyl sulfone as internal standard. [d]Incomplete conversion. ND=not determined.

Upon changing the Au(I) catalyst from Echavarren catalyst **22** to PPh_3AuNTf_2, a different ratio of products was observed and the major product of the reaction changes from formal S_N2' **100b** /S_N2 **116b** to the S_N2 + conjugate addition product **117b** respectively (Table

2.8, entries 1 and 2). Changing the oxidation state of the gold catalyst from I to III causes a significant decrease in the rate of the reaction: with Au(I) the reaction is completed within 10 minutes but with Au(III) only starting material was recovered (entry 3).

$InCl_3$ and $In(OTf)_3$ produced significantly better results (47% and 44% **100b** respectively), as In(III)-catalysis appears to be much more selective for the formal S_N2' product **100b** and no formal S_N2 **116b** was observed (entries 5-6). InI_3, although still selective for the formal S_N2' **100b**, gave a lower yield of 31% (entry 7).

Other Lewis acids were significantly less effective with yields <10% for the formal S_N2' product **100b** (entries 8-14).

It can be concluded that $InCl_3$ appears to be the most effective Lewis acid for this reaction (45% of **100b**) closely followed by $In(OTf)_3$ (44% of **100b**) and the Echavarren catalyst **22** with an overall yield of 55% (**100b** + **116b**).

The reaction was then optimised for $InCl_3$ and it was shown that the optimised reaction conditions for the Echavarren catalyst **22** were also the optimum conditions for $InCl_3$ (Table 2.9).

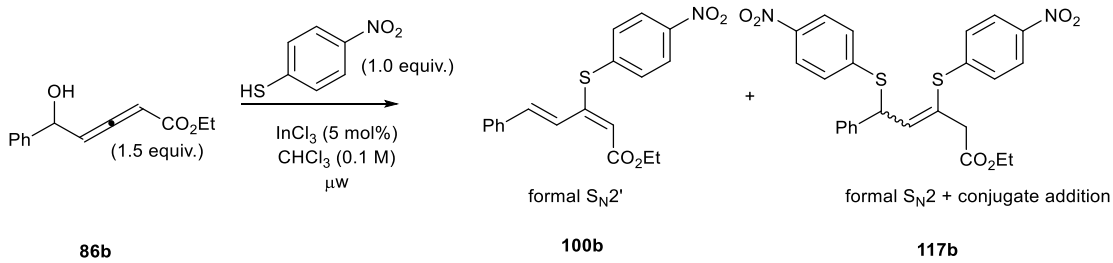


Table 2.9: $InCl_3$ optimisation

Entry	Time (min)	Solvent	Temp (°C)	100b:117b	Yield S_N2' 100b
1[a]	10	Toluene	70	5:1	45%[b]
2	10	Dioxane	70	-	-
3[a]	10	DCE	70	10:1	44%[b]
4	10	Methylated spirits	70	5:2	20%[b]
5	10	$CHCl_3$	35	5:1	Complex mixture
6	5	$CHCl_3$	50	5:1	25%[b]
7	5	$CHCl_3$	70	10:1	49%[c]

[a] Incomplete conversion [b] Yield obtained by NMR analysis using dimethyl sulfone as an internal standard [c] Isolated yield.

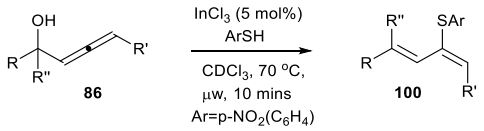
As with the previous Au(I) optimisation, $CHCl_3$ is the most effective solvent for the reaction and again lower temperatures give a complex mixture products (Table 2.9, entry 5) whereas 70 °C gives a 49% yield (entry 7).

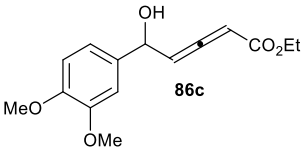
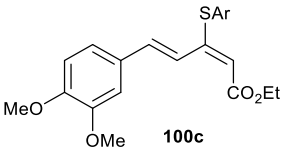
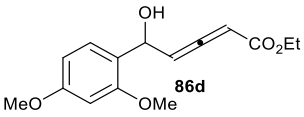
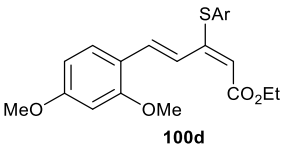
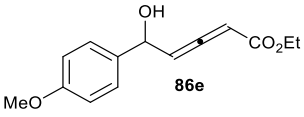
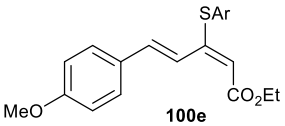
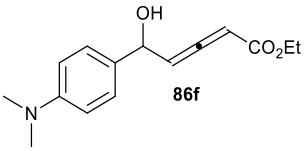
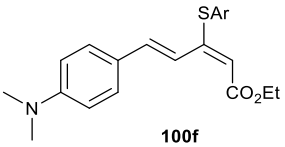
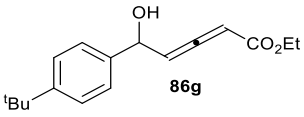
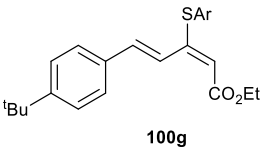
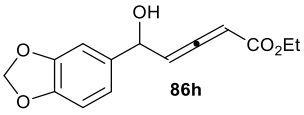
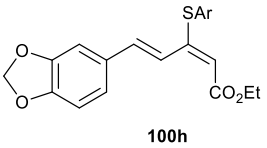
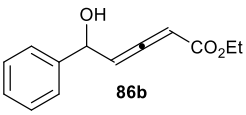
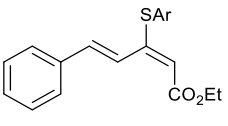
As with gold(I),[24] $InCl_3$ is also known to catalyse the cyclisation of enynes[25] and being a soft Lewis acid, it is also able to activate π-bonds including alkenes and alkynes.[25-26] Advantages of $InCl_3$, include lower cost compared to gold, lower heterophilicity, and air and water stability (see section 1.5 for more information on In(III) catalyst).[27]

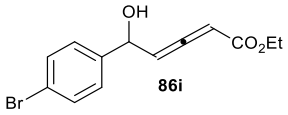
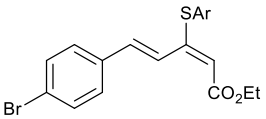
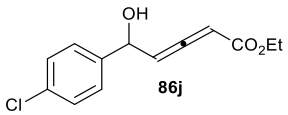
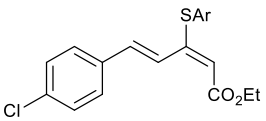
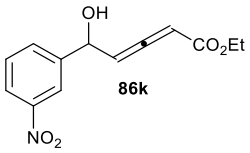
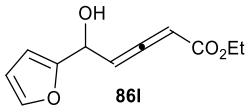
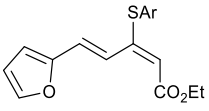
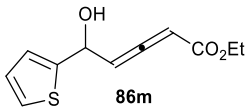
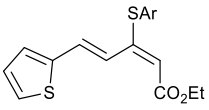
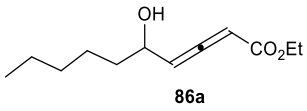
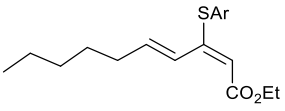
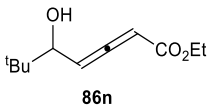
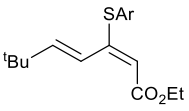
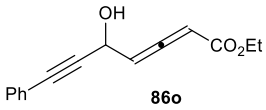
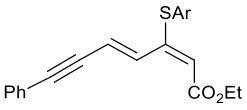
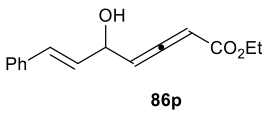
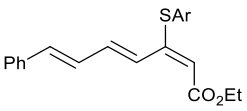
2.3.3 Substrate Scope

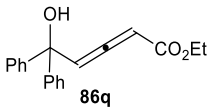
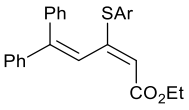
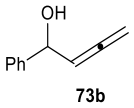
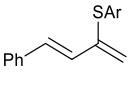
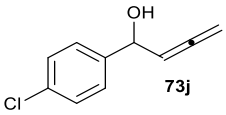
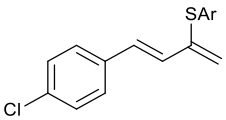
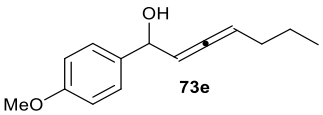
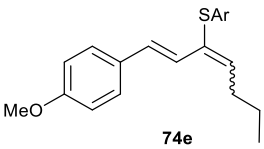
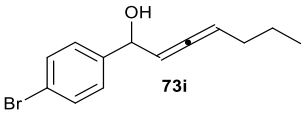
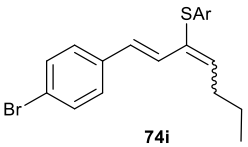
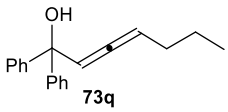
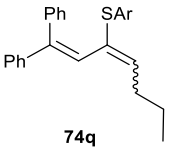
Following on from these results an allenol substrate scope was carried out (Table 2.10)

Table 2.10**:** Allenol Scope



Entry	**86**	**100**	Yield (%)[a]
1	 **86c**	 **100c**	80% *(Au(I):[d] <5%[e])*
2	 **86d**	 **100d**	96%[b]
3	 **86e**	 **100e**	79%[c]
4	 **86f**	 **100f**	90%
5	 **86g**	 **100g**	68%[c] *(Au(I):[d] 5:2* ***100g*****:*****116g*****,** *28%* ***100g****)*
6	 **86h**	 **100h**	47%
7	 **86b**	 **100b**	49% *(Au(I)[d] 1:1* ***100b*****:*****116b*****,** *38%* ***100b*** *34%* ***116b****)*

8	 **86i**	 **100i**	93%[c]
9	 **86j**	 **100j**	49%
10	 **86k**	No reaction	0% *(Au(I):[d]* *no reaction)*
11	 **86l**	 **100l**	79%[c]
12	 **86m**	 **100m**	84[c]
13	 **86a**	 **100a**	42[h,i]
14	 **86n**	 **100n**	80[f] *(Au(I):[d] <5%[e])*
15	 **86o**	 **100o**	85[c] 4:1 *E*/*Z* *(Au(I):[d]* *no reaction)*
16	 **86p**	 **100p**	38[c]

17	 **86q**	 **100q**	100
18	 **73b**	 **74b**	72[h,j] *(Au(I):[d] <5%[e])*
19	 **73j**	 **74j**	91[h]
20	 **73e**	 **74e**	88[k,l]
21	 **73i**	 **74i**	77[k,l]
22	 **73q**	 **74q**	59[h,m]

[a]Isolated yields. 0.07 mmol scale of ArSH and 0.105 mmol of **86**. [b]Same result when repeated with only 1 mol% $InCl_3$, 0.36 mmol scale of ArSH. [c]90 °C, 20 min. [d]Cat. **22** (5 mol%), 70 °C, 30 min, sealed tube. [e]Complex mixture of products. [f]90 °C, 30 min. [g]Recovered starting material. [h]90 °C for 60 min. [i]Product **116** also observed in 31%. [j]5:1 **100:116.** [k]90 °C, 18 h, sealed tube. [l]2:1 *EE*:*EZ*. [m]1:1 *E*:*Z*

Initially, substituents on the aryl ring were varied. Allenols which contained electron-rich aryl substituents, including *O*- and *N*-alkyl substitutions, *ortho*, *meta*, and *para*, worked well and produced the desired formal S_N2' product in good to excellent yields, 68-96% (entries 1-5). The exception to this was the 1,3-benzodioxole derivative **86h** which still produced the desired product **100h** but in a moderate yield of 47% (entry 6). Slightly electron-withdrawing aryls which contain a chloro- or a bromo- substituent still perform well with excellent (93%) to moderate (49%) yields respectively (entries 8 and 9). However, very electron-withdrawing aryls do not react under these conditions (entry 10). Allenols containing heterocycles including furan and thiophene substituents produce

the formal S_N2' product in excellent yields, 79-84%, respectively (entries 11-12). Alkyl R groups on the allenol are also tolerated with the ^{t}Bu group performing much better (80%) than an alkyl chain (42%) (entries 13-14).

Next, the chemoselectivity of the reaction was investigated. Allenol **86o** containing an alkyne reacted chemoselectively to produce the ynediene **100o** in an excellent yield with no reaction observed at the alkyne (entry 15, 85%). However, the *EE*/*EZ* ratio decreased to 4:1 for this particular substrate. Allenol with pendent alkene **86p** reacted selectively at the allene to produce the triene product **100p** albeit with a modest yield (entry 16, 38%). Tertiary allenol **86q** also reacted well to produce the desired diene **100q** in quantitative yield (entry 17). It should be noted that lowering the $InCl_3$ catalyst loading from 5 mol% to 1 mol% and increasing the scale of the reaction from 0.105 mmol to 0.57 mmol of **86d** is not detrimental to the reaction (**100d** still formed in 96% yield, Entry 2, Table 2.10). The crystal structure of **100b** confirms the *E,E* stereochemistry indicated by NOESY analysis for this series of dienes (Figure 2.2).

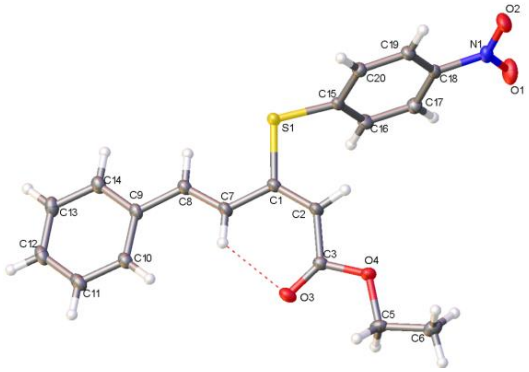


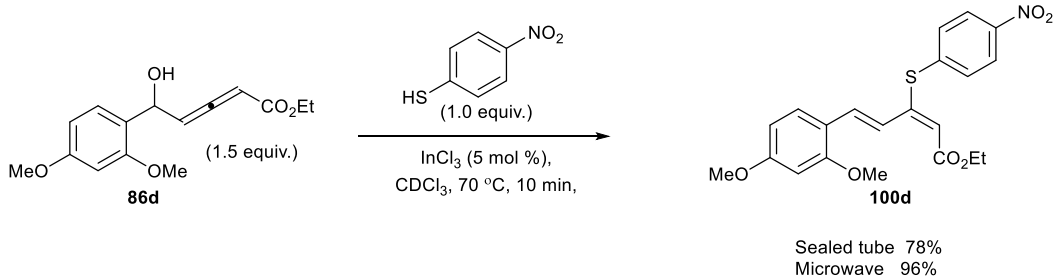
Figure 2.2: Crystal structure of **100b**.

Next, allenols lacking the ester substituent were screened to determine whether the ester group is required for good selectivity and reactivity. The reaction proceeds efficiently without the ester group when R' is replaced with H (**73b** and **73j**, entries 18-19) or indeed with ^{n}Pr (**73e**, **73f** and **73q**, entries 20-22). Although these substrates required higher temperatures and increased reaction times for good conversions, the formal S_N2' product was still obtained. When R'=H, dienes **74b** and **74j** were produced in good (72%, entry 18) to excellent (91%, entry 19) yields. However product **74j** was very unstable and decomposed within an hour at room temperature. When R' is an alkyl chain, the reaction worked equally well with electron-rich (88%, entry 20), electron-poor (77%, entry 21) and tertiary allenols (59%, entry 22). However, **74e**-**74q** are formed in poor *EE*:*EZ* ratio

(2:1 and 1:1). This was thought to be due to the fact that **74e-74q** were found not to be configurationally stable, with the *EE*:*EZ* ratio changing over the characterisation period.

There have been several papers comparing the use of gold and indium catalysis in recent years.[28] Therefore, Au(I) catalyst **22** was evaluated alongside In(III) for selected substrates. After performing several reactions in the microwave it was determined that, for this reaction with Au(I) catalyst **22**, the results were not consistent and therefore, a reoptimisation of conditions for **86b** under gold-catalysis was carried out. It was shown that a temperature of 70 ^{o}C for 30 minutes in a sealed tube provided the highest yields, but with poor regioselectivity (1:1 **100b**:**116b**, 38%:34% entry 7, Table 2.10). This is consistent with initial experiments. The reaction of allenol **86g** to give the formal S_N2' diene product **100g** occurred but also with poor selectivity (5:2 **100g**:**116g**, entry 5). The use of gold catalyst **22** with other substrates either resulted in no reaction (entries 10 and 15) or a complex mixture of products (entries 1, 14 and 18). It can therefore be concluded for this reaction, In(III) proves to be a far superior catalyst than Au(I) in terms of both regioselectivity and yield.

It should be noted that microwave heating (microwave containing an external surface sensor) was adopted for ease of use and to heat the $InCl_3$-catalysed reaction above the boiling point of $CHCl_3$. The reaction can also be carried out in a sealed tube under conventional heating, but the microwave heating was chosen as it is more practical from a safety point of view (for temperatures above the boiling points of solvents) and the isolated yields are also improved (Scheme 2.24).

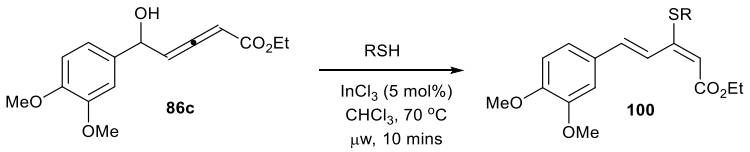


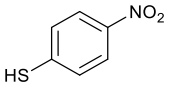
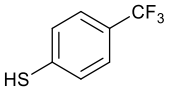
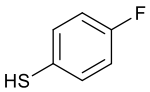
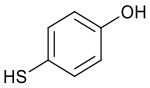
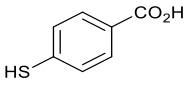
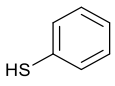
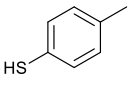
Scheme 2.24: Microwave heating *vs* thermal heating

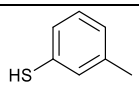
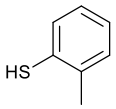
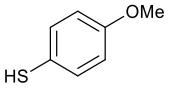
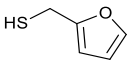
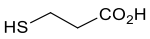
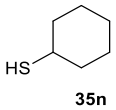
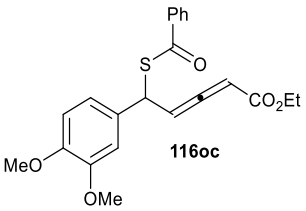
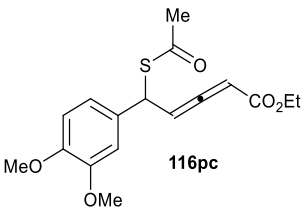
2.3.4 Thiol Nucleophile Scope

Next, the thiol nucleophile scope was investigated using allenol **86c** as a model substrate under $InCl_3$ catalysis (Table 2.11).

Table 2.11: Thiol Screen



Entry	RSH	Product	Yield (%)
1	 **35b**	**100bc**	80
2	 **35c**	**100cc**	74
3	 **35d**	**100dc**	65
4	 **35e**	**100ec**	29[b]
5	 **35f**	**100fc**	<9[c]
6	 **35a**	**100ac**	73
7	 **35g**	**100gc**	72

8	 35h	**100hc**	54
9	 35i	**100ic**	75
10	 35j	**100jc**	52
11	 35k	**100kc**	52
12	 35l	**100lc**	52
13	 35m	**100mc**	40
14	 35n	**100nc**	45
15	 35o	 116oc	66[e]
16	 35p	 116pc	52[f]

[a]Isolated yields. 0.07 mmol scale of RSH and 0.105 mmol of **86**. [b]90 °C, 60 min, [c]Co-elutes with starting material. [e]1:2 dr. [f]1:0.7 dr.

Electron-poor thiophenols containing strongly electron-withdrawing groups such as NO_2, CF_3, and F (entries 1-3, 65-80%) perform much better than thiophenols containing strongly electron donating substituents (entry 10, 52%). The exception to this is entry 5

where the substituent CO_2H is electron-withdrawing and a severe drop in yield is observed (9%). The low yields with **35e** and **35f** may be due to the presence of acidic protons which would disrupt the hydrogen bonding required in the mechanism. Slightly electron-rich thiophenols, containing *ortho*, *para* and *meta* substitution, as well as thiophenol were tolerated with moderate to good yields 54-75% (entries 6-9).

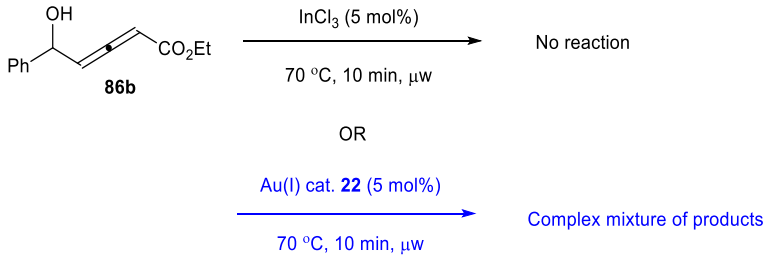
The use of alkyl thiols as nucleophiles were also investigated. Primary and secondary alky thiols were tolerated producing the desired dienes in moderate yields (40-52%, entries 11-14). The presence of a furan (entry 12, 52%) and a carboxylic acid (entry 13, 40%) are also tolerated but again the presence of an acidic proton in **35m** causes a drop in yield.

Finally, thioacids were investigated. Interestingly, the opposite regioselectivity was observed using these nucleophiles, forming the formal S_N2 product **116** in good yields 52-66% (entries 15 and 16). No isomerisation from the formal S_N2 product **116** to the formal S_N2' product was observed, implying that **116** is the thermodynamic product (see section 2.3.5).

2.3.5 Mechanistic Studies and Control Reactions

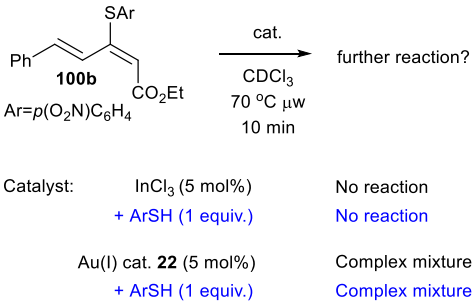
Several control reactions were carried out in order to shed some light on the mechanism of the reaction. Firstly the reaction with allenol **86b** was carried out in the absence of catalyst. After 10 minutes at 70 ^oC, no reaction had occurred and only starting material was recovered. This suggests that the formation of the formal S_N2' diene product does indeed require a catalyst under these conditions.

Due to the propensity of allenols to undergo intramolecular cyclisation reactions as mentioned previously, it was necessary to perform a control reaction in the absence of a thiol nucleophile (Scheme 2.25). When this reaction was investigated with allenol **86b** under $InCl_3$ catalysis, no reaction was observed. However, when this same reaction was repeated with Au(I) catalyst **22**, allenol **86b** is consumed to form a complex mixture of products in the absence of any thiol nucleophiles (Scheme 2.25).



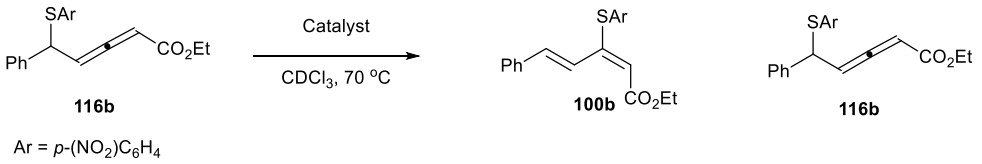
Scheme 2.25: Control experiment – no thiol nucleophile added

Next, the formal S_N2' product **100b** was resubjected to the original reaction conditions under both $InCl_3$ and Au(I) catalysis (Scheme 2.26). Under $InCl_3$ catalysis no reaction was observed, with or without thiol present. This suggests that the formal S_N2' product is stable in the presence of In(III). In contrast, under Au(I)-catalysis, a complex mixture of products was obtained suggesting the Au(I)-catalyst reacts further with the product to produce a complex mixture products. This may provide some clues as to why the $InCl_3$ catalysed reactions produce the desired diene in much higher yields.



Scheme 2.26: Formal S_N2' product resubjected to original reaction conditions under In(III) and Au(I) catalysis

The Lee group have recently shown that thioetherification reactions of allylic alochols under Au(I) catalysis is under equilibrium control as discussed in section 2.1.[7] Therefore, the behaviour of the formal S_N2 product **116b** was investigated under the reaction conditions in order to gain insight into the mechanism (Scheme 2.27).

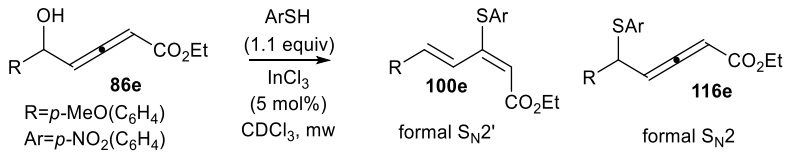


Conditions:	$InCl_3$ (5 mol%), μw	5 min	1:3 **100b**:**116b**
		30 min	1:1 **100b**:**116b**
		1.5 h	5:1 **100b**:**116b**
		3 h	**100b only**
	+ ArSH (1 equiv.)	**5 min**	**100b only**
	Au(I) cat. **22** (5 mol%)	30 min	1:1 **100b**:**116b**
		1.5 h	1:1 **100b**:**116b**
		16 h	1:1 **100b**:**116b** + decomposition
	+ ArSH (1 equiv.)	30 min	decomposition

Scheme 2.27: Resubjection of the formal S_N2 product **116b** to reaction condtions

Under In(III)-catalysis the formal S_N2 product **116b** slowly isomerises over a period of three hours to produce the desired 1,3-diene **100b** (formal S_N2' product) in the absence of a thiol nucleophile. However, if one equivalent of the thiol nucleophile was added to the reaction mixture, the reaction proceeded much faster and completion occurred within 5 minutes. In contrast, under Au(I)-catalysis, the ratio of the formal S_N2' product **100b** to the formal S_N2 product **116b** remained unchanged even after 16 h at which point, signs of decomposition occurred. As with the In(III)-catalysed reaction, the addition of 1 equivalent of a thiol nucleophile increased the rate of the reaction and led to decomposition within 30 minutes.

With several different substrates it was noted that, in order for the reaction to be regioselective for the formal S_N2' product, higher temperatures were needed. Therefore, the effects of temperature on regioselectivity were also investigated to gain mechanistic insight (Scheme 2.28).



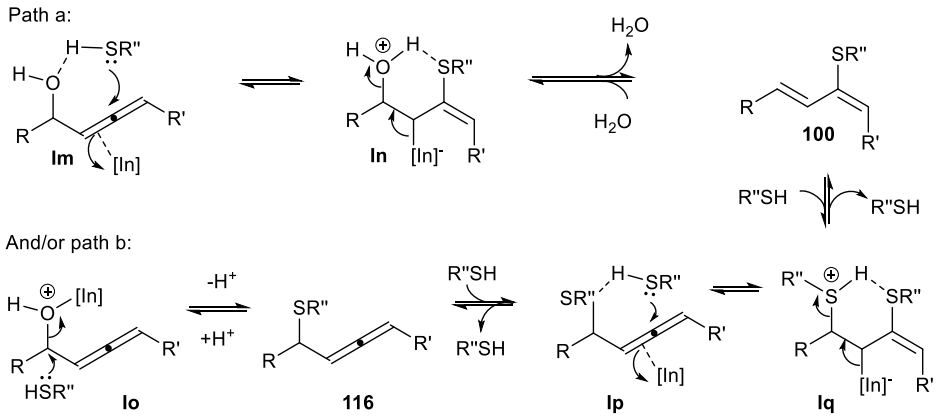
[a]Isolated yields
[b]Incomplete conversion

90 °C, 20 mins	>20:1 **100e**:**116e** (79% **100e**)[a]
70 °C, 10 mins	1:1 **100e**:**116e** (30% **100e**, 30% **116e**)[a]
35 °C, 20 mins	1:1.3 **100e**:**116e** (7% **100e**, 11% **116e**)[a,b]

Scheme 2.28: The effects of temperature on regioselectivity

For allenol **86e** under standard reaction conditions (70 °C for 10 mins) a 1:1 mixture of **100e**:**116e** was produced. However, at higher temperatures of 90 °C the reaction becomes more selective and favours the formation of the desired formal S_N2' product **100e**. At lower temperatures of 35 °C the reaction does not proceed to completion and favours the formal S_N2 product **116e**.

With these results in mind, plausible mechanisms are proposed (Scheme 2.29). $InCl_3$ has been shown to activate both soft C-C multiple bonds and the O-centre, therefore, two possible pathways are presented. In pathway a, In(III) activates the allenol towards nucleophilic attack potentially aided by hydrogen bonding (**Im**). This then forms a six membered ring (**In**) where the catalyst and water are eliminated to produce the 1,3-diene (formal S_N2') product. Alternatively, in pathway b, the indium catalyst activates the alcohol for displacement by the thiol nucleophile (**Io**), resulting in the formal S_N2 product **116**. The indium catalyst can then activate the allenol for a second attack by thiol (**Ip**) and proceed through intermediate **Iq**, to give the formal S_N2' product by isomerisation.

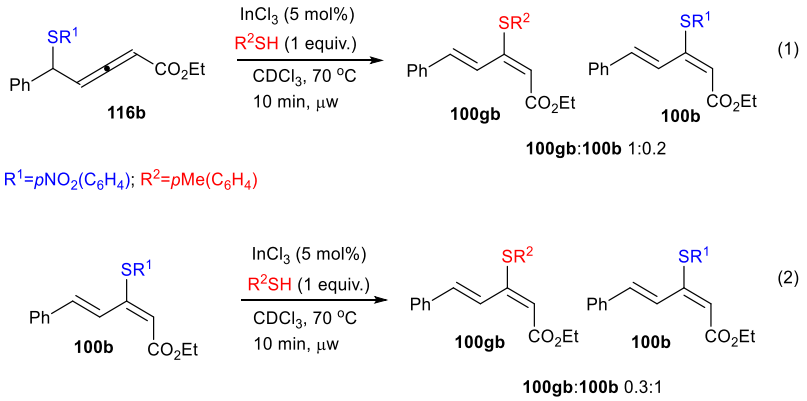


Scheme 2.29: Plausible mechanism

At high temperatures the reaction can proceed either directly through pathway a or high temperatures encourage the isomerisation *via* pathway b. However, both pathways could be occurring and the favoured pathway may be substrate dependent.

In order to determine whether the reaction was indeed operating through pathway b, crossover experiments were investigated (Scheme 2.30). When the formal S_N2 product **116b** was resubjected to reaction conditions with a different thiol nucleophile, isomerisation to the 1,3-diene incorporated both thiols (Equation 1, Scheme 2.30). Comparatively, when the formal S_N2' product **100b** was resubjected to the same reaction,

again incorporation of second the thiol nucleophile is observed (Equation 2, Scheme 2.30). This suggests that pathway b could be operating and that the reaction is reversible.



Scheme 2.30: Crossover experiments

2.4 Conclusions

An intermolecular formal S_N2' addition of a thiol nuclophile to an allenol has been successfully developed. After several screens of gold catalysts and counterions it was found that gold was not the optimum catalyst for this reaction. However, after a successful Lewis acid screen, $InCl_3$ was found to be a far superior catalyst.

The reaction occurs with a variety of substrates including substrates with electron-rich and electron-poor aryls, heterocycles, and alkyl groups as well as several other examples, most of which are selective for the *EE* isomer. The reaction was also found to be chemoselective with an internal alkyne and alkene remaining unaffected.

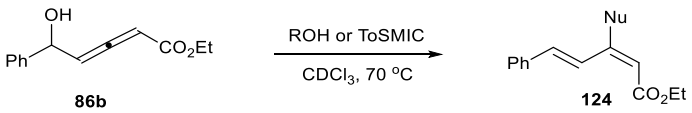
A wide range of nucleophiles was also investigated. The reaction showed tolerance for electron-poor, neutral and slightly electron-rich thiophenols. However, strongly electron rich thiophenols and thiols containing an acidic proton caused a decrease in yield. Surprisingly, thioacids, although competent nucleophiles, gave the opposite regioselectivity with the formal S_N2 product being preferred.

$InCl_3$ was found to be a far superior catalyst than Au(I). When our control studies were performed it was found that the products in the presence of Au(I) were unstable and further reacted to produce unidentified products. In contrast, the 1,3-diene products were found to be stable in the presence of $InCl_3$.

Further mechanistic studies suggest that the regioselectivity of the reaction is under equilibrium control and is determined by the thermodynamic stability of the products.

2.5 Future work

The obvious extension to this work would be to explore other nucleophiles. Unfortunately, initial attempts with alcohol and isocyanide nucleophiles were unsuccessful (Scheme 2.31). However, more exploratory studies should be carried out in future to further explore this area.

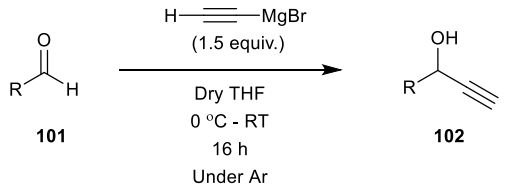


Scheme 2.31: Future work

Considering the superior performance of $InCl_3$ *vs* Au(I) in this project, it would also be interesting to re-investigate our earlier allylic alcohol substrates and compare indium(III) *vs* gold(I) catalysts, particularly with substrates where gold(I) gave low yields or a complex mixture of products. This work is described in Chapter 3.

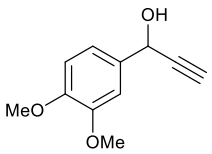
2.6 Experimental

Preparation of propargylic alcohols



To the aldehyde (14 mmol, 1 equiv.), in a dry flask, was added dry THF and ethynyl magnesium bromide (0.5 M THF, 21 mmol, 1.5 equiv.) was added dropwise over 30 minutes at 0 °C. The mixture was kept at this temperature for 10 minutes then allowed to warm to room temperature. The reaction was stirred overnight at room temperature under argon. The organic layer was extracted with ethyl acetate and washed with a saturated solution of NH_4Cl and dried with $MgSO_4$. The solvent was removed and the desired product purified by column chromatography (hexane/ethyl acetate) to give propargylic alcohols.

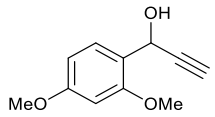
1-(3,4-Dimethoxyphenyl)prop-2-yn-1-ol (102c)[29]



The general procedure was followed to yield product **102c** as a pink solid (2.22 g, 11.6 mmol, 95%).

R_f 0.20 (3:1 hexane/ethyl acetate); Mp: 104-107 °C ($CDCl_3$) [Lit. mp 98-99 °C]; ν_{max}/cm^{-1} 3237 br (O-H) 2835 (C-H), 2110 (C≡C), 1517, 1468, 1452, 1436, 1416 (Ar C=C); ^1H NMR (300 MHz, $CDCl_3$), δ 7.09 (2H, m, Ar-H), 6.86 (1H, d, *J* = 3.8 Hz, Ar-H), 5.42 (1H, dd, *J* = 6.0, 2.2 Hz, HOC<u>H</u>), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 2.67 (1H, d, *J* = 2.2 Hz, C≡CH), 2.19 (1H, d, *J* = 6.1 Hz, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.3 (C), 149.2 (C), 132.7 (C), 119.0 (CH), 111.0 (CH), 109.8 (CH), 83.6 (C), 74.7 (CH), 64.3 (CH), 56.0 (CH_3), 55.9 (CH_3).

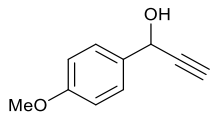
1-(2,4-Dimethoxyphenyl)prop-2-yn-1-ol (102d)[30]



Prepared using the general procedure but on a smaller scale, aldehyde (1.05 g, 6.31 mmol, 1 equiv.) and ethynyl magnesium bromide (0.5 M THF, 9.48 mmol, 1.5 equiv.) was used to yield **102d** as a brown oil (1.20 g, 6.25 mmol, 99%).

R_f 0.38 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3285 br (O-H) 2837 (C-H), 2110 (C≡C), 1610, 1587, 1504, 1455, 1438, 1419 (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (1H, d, *J* = 8.1 Hz, Ar-H), 6.40-6.45 (2H, m, Ar-H), 5.64 (1H, dd, *J* = 6.2, 2.2 Hz, C<u>H</u>OH), 3.84 (3H, s, OMe), 3.80 (3H, s, OMe), 2.96 (1H, d, *J* = 6.2 Hz, CHO<u>H</u>), 2.60 (1H, d, *J* = 2.2 Hz, C≡C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.2 (C), 157.8 (C), 128.7 (CH), 121.1 (C), 104.3 (CH), 98.9 (CH), 83.5 (C), 73.9 (CH), 60.4 (CH), 55.6 (CH_3), 55.4 (CH_3).

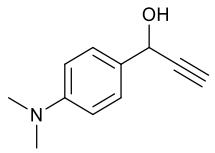
1-(4-Methoxyphenyl)prop-2-yn-1-ol (102e)[31]



Prepared using the general procedure but on a smaller scale, aldehyde (1.17 g, 8.60 mmol, 1 equiv.) and ethynylmagnesium bromide (0.5 M THF, 12.9 mmol, 1.5 equiv.) was used to yield **102e** as a brown oil (1.34 g, 8.27 mmol, 96%).

R_f 0.45 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3394 br (O-H) 2837 (C-H), 2115 (C≡C), 1587, 1509, 1463, 1441, 1421, (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (2H, d, *J* = 8.4 Hz, Ar-H), 6.90 (2H, d, *J* = 8.4 Hz, Ar-H), 5.38 (1H, d, *J* = 2.2 Hz, C<u>H</u>OH), 3.80 (3H, s, OMe), 2.73 (1H, bs, OH), 2.66 (1H, d, *J* = 2.2 Hz, C≡C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.7 (C), 132.5 (C), 128.1 (CH), 114.0 (CH), 83.8 (C), 74.6 (CH), 63.9 (CH), 55.4 (CH_3).

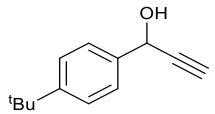
1-(4-(Dimethylamino)phenyl)prop-2-yn-1-ol (102f)



Prepared using the general procedure but on a smaller scale, aldehyde (1.10 g, 7.44 mmol, 1 equiv.) and ethynylmagnesium bromide (0.5 M THF, 11.2 mmol, 1.5 equiv.) was used to yield **102f** as a green solid (1.19 g, 6.80 mmol, 92%).

R_f 0.46 (3:1 hexane/ethyl acetate); Mp: 71-76 ^oC ($CDCl_3$); ν_{max}/cm^{-1} 3420 br (O-H) 2881 (C-H), 2111 (C≡C), 1566, 1521, 1478, 1441 (Ar C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40 (2H, d, *J* = 8.8 Hz, Ar-H), 6.72 (2H, d, *J* = 8.8 Hz, Ar-H), 5.35 (1H, dd, *J* = 5.6, 2.2 Hz, C<u>H</u>OH), 2.95 (6H, s, NMe_2), 2.78 (1H, d, *J* = 5.6 Hz, O<u>H</u>), 2.65 (1H, d, *J* = 2.2 Hz, C≡C<u>H</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.8 (C), 128.4 (C), 127.9 (CH), 112.7 (CH), 84.3 (C), 74.2 (CH), 64.1 (CH), 40.7 (CH_3).

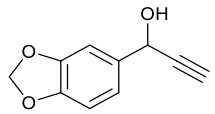
1-(4-*tert*-Butylphenyl)prop-2-yn-1-ol (102g)[32]



Prepared using the general procedure but on a smaller scale, aldehyde (1.05 g, 6.53 mmol, 1 equiv.) and ethynylmagnesium bromide (0.5 M THF, 9.80 mmol, 1.5 equiv.) was used to yield **102g** as a brown oil (1.22 g, 6.50 mmol, 100%).

R_f 0.60 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3370 br (O-H) 2961 (C-H), 2117 (C≡C), 1510, 1475, 1462 1446, 1409 (Ar C=C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.49 (2H, d, *J* = 8.3 Hz, Ar-H), 7.43 (2H, d, *J* = 8.4 Hz, Ar-H), 5.44 (1H, d, *J* = 2.2 Hz, C<u>H</u>OH), 2.66 (1H, d, *J* = 2.2 Hz, C≡C<u>H</u>), 1.35 (9H, s, ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 151.6 (C), 137.2 (C), 126.5 (CH), 125.7 (CH), 83.8 (C), 74.7 (CH), 64.2(CH), 34.6 (C), 31.7 (CH_3).

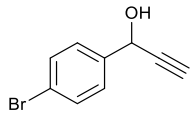
1-(Benzo[*d*][1,3]dioxol-5-ylprop-2-yn-1-ol) (102h)[31]



Prepared using the general procedure but on a smaller scale, aldehyde (349.3 mg, 2.30 mmol, 1 equiv.) and ethynylmagnesium bromide (0.5 M THF, 3.45 mmol, 1.5 equiv.) to yield product **102h** as a brown oil (317.6 mg, 1.80 mmol 79%).

R_f 0.49 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3400 br (O-H) 2895 (C-H), 2111 (C≡C), 1501, 1486, 1441 (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96-7.05 (2H, m, Ar-H), 6.76 (1H, d, *J* = 8.0 Hz, Ar-H), 5.95 (2H, s, OCH_2O), 5.30-5.38 (1H, m, C<u>H</u>OH), 2.69 (1H, d, *J* = 5.2 Hz, OH), 2.66 (1H, d, *J* = 2.2 Hz, C≡CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.9 (C), 147.8 (C), 134.1 (C), 120.4 (CH), 108.2 (CH), 107.4 (CH), 101.3 (CH_2), 83.6 (C), 74.5 (CH), 64.1 (CH).

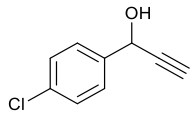
1-(4-Bromophenyl)pop-2-yn-1-ol (102i)[32]



Prepared using the general procedure but on a smaller scale, aldehyde (1.03 g, 5.60 mmol, 1 equiv.) and ethynylmagnesium bromide (0.5 M THF, 8.39 mmol, 1.5 equiv.) to yield product **102i** as an oil (1.11g, 5.26 mmol 94%).

R_f 0.53 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3292 br (O-H) 2975 (C-H), 2116 (C≡C), 1485, 1401 (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.5 Hz, Ar-H), 7.36 (2H, d, *J* = 8.5 Hz, Ar-H), 5.36 (1H, d, *J* = 2.2 Hz, C<u>H</u>OH), 3.21 (1H, br s, OH), 2.66 (1H, d, *J* = 2.2 Hz, C≡C<u>H</u>) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.0 (C), 131.8 (CH), 128.4 (CH), 122.5 (C), 83.1 (C), 75.3 (CH), 63.6 (CH).

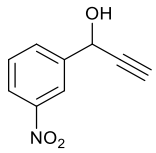
1-(4-Chlorophenyl)prop-2-yn-1-ol (102j)[33]



General procedure was followed to yield product **102j** as a brown oil (1.70 g, 10.2 mmol, 84%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1)

R_f 0.55 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3294 br (OH), 2119 (C≡C), 1596, 1489 (Ar C=C), 789 (C-Cl); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.43 (2H, d, *J* = 8.4 Hz, Ar-H), 7.33 (2H, d, *J* = 8.6 Hz, Ar-H), 5.39 (1H, d, *J* = 2.2 Hz, C<u>H</u>OH), 3.84 (1H, bs, OH), 2.70 (1H, d, *J* 2.2Hz, C≡CH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.4 (C), 134.3 (C), 128.8 (CH), 128.0 (CH), 83.1 (C), 75.2 (CH), 63.7 (CH).

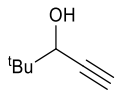
1-(3-Nitrophenyl)prop-2-yn-1-ol (102k)[13]



General procedure was followed to yield product **102k** as a yellow oil (418 mg, 2.36 mmol, 18%). Purified by column chromatography (eluent: hexane/ethyl acetate, 10:1 to 5:1)

R_f 0.14 (3:1 hexane/ethyl acetate) ν_{max}/cm^{-1} 3289 br (OH), 2219 (C≡C), 1523 (NO_2), 1478, 1439 Ar C=C), 1346 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.44 (1H, m, Ar-H), 8.21 (1H, m, Ar-H), 7.90 (1H, m, Ar-H), 7.58 (1H, t, *J* = 8.0 Hz, Ar-H) 5.58 (1H, dd, *J* = 6.0, 2.0 Hz, OHC<u>H</u>), 2.75 (1H, d, *J* = 2.0 Hz, C≡CH), 2.44 (1H, d, *J* = 6.0 Hz, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.5 (C), 141.9 (C), 132.6 (CH), 129.6 (CH), 123.4 (CH), 121.7 (CH), 82.3 (C), 74.7 (CH), 63.3 (CH).

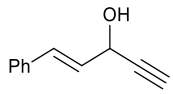
4,4-Dimethoxypent-1-yn-3-ol (102n)[35]



Prepared using the general procedure but on a smaller scale, aldehyde (1.11 g, 13.0 mmol, 1 equiv.) and ethynylmagnesium bromide (0.5 M THF, 19.4 mmol, 1.5 equiv.) to yield product **102n** as a brown oil (956 mg, 8.62 mmol 66%).

R_f 0.81 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3309 br (O-H) 2958, 2872 (C-H), 1724 (C≡C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.99 (1H, d, *J* = 2.0 Hz, C<u>H</u>OH), 2.42 (1H, d, *J* = 2.1 Hz, C≡C<u>H</u>), 2.20 (1H, bs, OH), 0.98 (9H, s, ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 83.6 (C), 73.7 (CH), 71.1 (CH), 35.6 (C), 25.1 (CH_3).

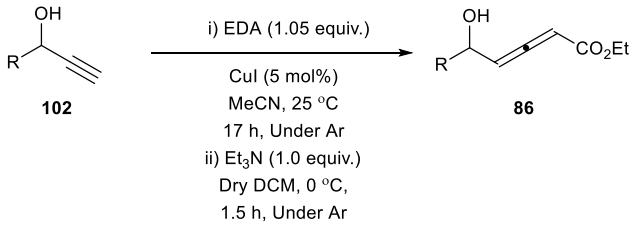
(*E*)-1-Phenylpent-1-en-4-yn-3-ol (102p)[32]



Prepared using the general procedure but on a smaller scale, aldehyde (1.06 g, 8.04 mmol, 1 equiv.) and ethynylmagnesium bromide (0.5 M THF, 12.0 mmol, 1.5 equiv.) to yield product **102p** as an oil (1.25 g, 7.90 mmol 99%).

R_f 0.50 (3:1 hexane/ethyl acetate) ν_{max}/cm^{-1} 3392 (OH), 3267, 3025 (C-H), 2120 (C≡C), 1575 (C=C), 1492, 1451, 1397 (Ar C=C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16-7.38 (2H, m, Ar-H), 7.15-7.31 (3H, m, Ar-H), 6.73 (1H, dd, *J* = 1.3, 15.8 Hz, PhC<u>H</u>=CH)), 6.23 (1H, dd, *J* = 15.8, 5.9 Hz, PhCH=C<u>H</u>), 4.99 (1H, dt, *J* = 5.9, 2.2 Hz, C<u>H</u>OH), 2.56 (1H, d, *J* = 2.2 Hz, C≡C<u>H</u>), 2.03 (1H, br s, OH); ^{13}C NMR (300 MHz, $CDCl_3$) δ 136.0 (C), 132.5 (CH), 128.8 (CH), 128.4 (CH), 127.6 (CH), 127.0 (CH), 82.9 (C), 74.8 (CH), 62.9 (CH).

Preparation of Allenols from Propargylic Alcohols



General Procedure A *(when triethylamine is required):*

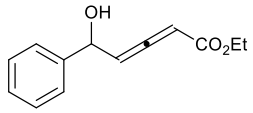
To the propargylic alcohol (1.30 mmol, 1 equiv.), in a dry flask, was added dry MeCN (1M), CuI (5 mol%), and EDA (1.30 mmol, 1 equiv.) The reaction was stirred at 25 °C overnight under argon. The reaction mixture was filtered through a plug of glass wool and washed with diethyl ether. The solvent was then removed and the crude was dissolved in dry DCM (0.2 M) and Et_3N (1.2 equiv.) was added and stirred at 0 °C for 1 h. The solvent was removed and the crude mixture was purified by column chromatography (hexane/ethyl acetate) to give allenic alcohols **86** as product.[13]

General Procedure B *(when triethylamine is not required):*

To the propargylic alcohol (1.30 mmol, 1 equiv.), in a dry flask, was added dry MeCN (1 M), CuI (5 mol%), and EDA (1.30 mmol, 1 equiv.) The reaction was stirred at 25 °C overnight under argon. The reaction mixture was filtered through a plug of glass wool and washed with diethyl ether. The solvent was removed and the crude mixture was purified by column chromatography (hexane/ethyl acetate) to give allenic alcohols **86** as product.[13]

Note: In our hands, the one-pot procedure described by Sabbasani *et al.*[13] was often low yielding and/or resulted in no reaction. Where this was the case, omitting triethylamine from the first step greatly improved the yields. In some cases, triethylamine was found to be unnecessary to form **86** (procedure B), in others, it was added in a second step as described above (procedure A) to isomerise any unwanted alkyne isomer to the allene **86**.

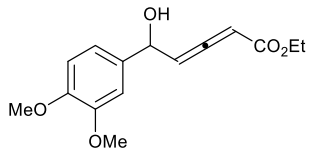
Ethyl 5-hydroxy-5-phenylpenta-2,3-dienoate (86b)[13]



General procedure A was followed to yield the title product **86b** as a yellow oil and a 1:1.4 mixture of diastereomers (415 mg, 1.90 mmol, 93%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1 to 3:1).

R_f 0.38 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3400 br (OH), 2982 (C-H), 1961 (C=C, allene), 1694 (C=O), 1493, 1450, 1421 (Ar C-C), 1156 (C-O-C), 748, 698 (*m*-C_6H_5); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.49 (2H + 2H', m, Ar-H), 7.28-7.41 (3H + 3H', m, Ar-H), 5.89 (1H + 1H', m, allene H), 5.78 (1H + 1H', m, allene H), 5.41 (1H + 1H', m, C<u>H</u>OH), 4.20 (2H + 2H', m, OCH_2), 2.43 (1H', bs, OH, minor), 2.36 (1H, bs, OH, major), 1.30 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 211.5 (C, minor), 211.4 (C, major), 165.9 (C, minor), 165.7 (C, major), 141.8 (C, major + minor), 128.6 (CH, minor), 128.5 (CH, major), 128.2 (CH, minor), 128.0 (CH, major), 126.4 (CH, minor), 126.1 (CH, major), 100.4 (CH, minor), 100.2 (CH, major), 90.8 (CH, major + minor), 71.5 (CH, minor), 71.4 (CH, major), 61.3 (CH_2, minor), 61.1 (CH_2, major), 14.2 (CH_3, major + minor).

Ethyl 5-(3,4-dimethoxyphenyl)-5-hydroxypenta-2,3-dienoate (86c)[13]

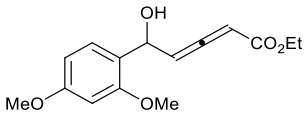


General procedure B was followed to yield product **86c** as a yellow oil and a 1:1 mixture of diastereomers (325 mg, 0.90 mmol, 90%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1 to 7:1 to 5:1 to 3:1 to 2:1).

R_f 0.29 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3474 br (OH), 2980 (C-H), 2836 (C-H), 1961 (C=C, allene), 1711 (C=O), 1593, 1513, 1463, 1415 (Ar C-C), 1256 (C-O-C), 1138 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00 (2H, m, Ar-H), 6.85 (1H, d, *J* = 8.2 Hz, Ar-H), 5.88 (1H, m, allene H), 5.78 (1H, m, allene H), 5.36 (1H, m, C<u>H</u>OH), 4.20 (2H, q, *J* = 7.1 Hz, OCH_2), 3.91 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 2.47 (1H, bs, OH), 1.28 (3H, m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.4 (C), 211.1 (C), 165.6 (C), 165.4 (C), 149.2 (C), 149.1 (C), 149.0 (C), 148.9 (C), 134.3 (C), 134.2 (C), 118.8 (CH), 118.5 (CH),

111.0 (CH), 110.9 (CH), 109.6 (CH), 109.3 (CH), 100.4 (CH), 100.2 (CH), 91.2 (CH), 90.8 (CH), 71.3 (CH), 71.2 (CH), 61.1 (CH_2), 61.0 (CH_2), 56.0 (2 x CH_3), 14.2 (2 x CH_3).

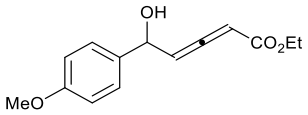
Ethyl 5-hydroxy-5-(2,4-dimethoxyphenyl)penta-2,3-dienoate (86d)



General procedure A was followed to yield product **86d** as a yellow oil and a 1:1 mixture of diastereomers (337 mg, 1.21 mmol, 89%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1 to 3:1).

R_f 0.40 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3400 br (OH), 3012 (C-H), 2836 (C-H), 1961 (C=C, allene), 1704 (C=O), 1588, 1505, 1464, 1416 (Ar C-C), 1260 (C-O-C), 1156 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (1H, d, *J* = 9.1 Hz, Ar-H), 7.27 (1H', d, *J* = 9.2 Hz, Ar-H), 6.42-6.49 (2H + 2H', m, Ar-H), 5.99 (1H, t, *J* = 6.0 Hz, allene H), 5.90 (1H', t, *J* = 6.0 Hz, allene H), 5.66-5.73 (1H + 1H', m, allene H), 5.52 (1H + 1H', m, C<u>H</u>OH), 4.09-4.21 (2H + 2H', m, OCH_2), 3.81 (3H + 3H', s, OCH_3), 3.78 (3H + 3H', s, OCH_3), 3.31 (1H, d, *J* = 6.4 Hz, OH), 3.15 (1H', d, *J* = 6.4 Hz, OH), 1.21-1.29 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.4 (C), 211.3 (C), 165.8 (C), 165.6 (C), 160.8 (C), 160.7 (C), 157.7 (C), 157.6 (C), 128.3 (CH), 128.0 (CH), 122.5 (2 x C), 104.34 (CH), 104.25 (CH), 99.8 (CH), 99.6 (CH), 98.7 (2 x CH), 90.7 (CH), 90.5 (CH), 67.7 (CH), 67.2 (CH), 60.9 (CH_2), 60.8 (CH_2), 55.43 (CH_3), 55.39 (CH_3), 14.23 (2 x CH_3), 14.21 (2 x CH_3); Found (FTMS+ p NSI) $[M + Na]^+$ 301.1040, $C_{15}H_{18}O_5Na$ requires 301.1046.

Ethyl 5-hydroxy-5-(4-methoxyphenyl)penta-2,3-dienoate (86e)

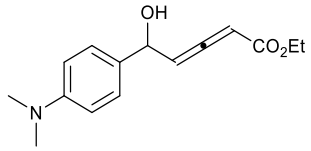


General procedure A was followed to yield product **86e** as a yellow oil and a 1:1 mixture of diastereomers (278 mg, 1.24 mmol, 78%). Purified by column chromatography (eluent: hexane/ethyl acetate 3:1).

R_f 0.33 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3426 br (OH), 2982 (C-H), 1961 (C=C, allene), 1711 (C=O), 1511, 1489, 1443 (Ar C-C), 1245 (C-O-C), 1171 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (2H, d, *J* = 8.8 Hz, Ar-H), 7.36 (2H, d, *J* = 8.8 Hz, Ar-H), 6.87

(2H, d, *J* = 8.6 Hz, Ar-H), 6.87 (2H, d, *J* = 8.7 Hz, Ar-H), 5.82-5.90 (1H + 1H', m, allene), 5.74 (1H + 1H', two overlapping t, *J* = 5.7, 5.9 Hz, allene), 5.36 (1H, m, C<u>H</u>OH), 5.30 (1H, m, C<u>H</u>OH), 4.12-4.25 (2H + 2H', m, OCH_2), 3.79 (3H + 3H', s, OCH_3), 3.28 (1H, d, *J* = 3.6 Hz, OH), 3.22 (1H, d, *J* = 3.8 Hz, OH), 1.28 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.40 (C), 211.39 (C), 165.9 (C), 165.8 (C), 159.5 (C), 159.4 (C), 134.0 (C), 133.9 (C), 127.8 (CH), 127.5 (CH), 114.0 (CH), 113.8 (CH), 100.5 (CH), 100.3 (CH), 90.8 (CH), 90.6 (CH), 71.0 (2 x CH), 61.2 (CH_2), 61.0 (CH_2), 55.3 (2 x CH_3), 14.2 (2 x CH_3); Found (FTMS+ p NSI) $[M + Na]^+$ 271.0936, $C_{14}H_{16}O_4Na$ requires 271.0941.

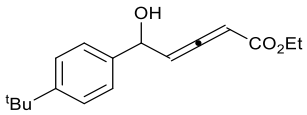
Ethyl 5-(4-(dimethylamino)phenyl)-5-hydroxypenta-2,3-dienoate (86f)



General procedure B was followed to yield product **86f** as a red/orange oil and a 1:1 mixture of diastereomers (147 mg, 0.56 mmol, 39%). Purified by column chromatography (eluent: hexane/ethyl acetate 3:1).

R_f 0.28 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3400 br (OH), 2981 (C-H), 1959 (C=C, allene), 1710 (C=O), 1521, 1477, 1444, 1413 (Ar C-C), 1252 (C-O-C), 1157 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (2H + 2H', t, *J* = 8.5 Hz, Ar-H), 6.72 (2H + 2H', d, *J* = 8.2 Hz, Ar-H), 5.87 (1H + 1H', m, allene H), 5.70-5.84 (1H + 1H', m, allene H), 5.35 (1H, m, C<u>H</u>OH), 5.28 (1H', m, C<u>H</u>OH), 4.14-4.27 (2H + 2H', m, OCH_2), 2.95 (6H, s, NMe_2), 2.94 (6H', s, NMe_2), 2.35 (1H + 1H', m, OH), 1.26-1.35 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.33 (C), 211.26 (C), 165.8 (C), 165.6 (C), 150.7 (C), 150.6 (C), 129.48 (C), 129.42 (C), 127.6 (CH), 127.2 (CH), 112.5 (CH), 112.4 (CH), 100.5 (CH), 100.3 (CH), 91.0 (CH), 90.7 (CH), 71.3 (2 x CH), 61.04 (CH_2), 60.98 (CH_2), 40.59 (CH_3), 40.57 (CH_3), 14.3 (2 x CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 262.1441, $C_{15}H_{20}NO_3$ requires 262.1438.

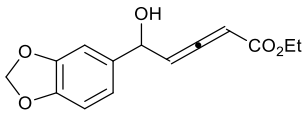
Ethyl 5-(4-*tert*-butylphenyl)-5-hydroxypenta-2,3-dienoate (86g)



General procedure A was followed to yield product **86g** as a yellow oil and a 1:1 mixture of diastereomers (236 mg, 0.86 mmol, 63%). Purified by column chromatography (eluent: hexane/ethyl acetate 7:1 to 5:1).

R_f 0.63 (hexane/ethyl acetate 3:1); ν_{max}/cm^{-1} 3400 br (OH), 2962 (C-H), 1960 (C=C, allene), 1713 (C=O), 1509, 1463, 1408 (Ar C-C), 1254 (C-O-C), 1157 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (4H + 4H', m, Ar-H), 5.83-5.92 (1H + 1H', m, CHC<u>H</u>=C=CH), 5.77-5.80 (1H, m, CHCH=C=C<u>H</u>), 5.74-5.77 (1H', m, CHCH=C=C<u>H</u>), 5.37-5.43 (1H, m, C<u>H</u>OH), 5.31-5.37 (1H', m, C<u>H</u>OH), 4.11-4.27 (2H + 2H', m, OCH_2), 3.07 (1H', d, *J* = 4.0 Hz, OH), 2.96 (1H, d, *J* = 4.1 Hz, OH), 1.26-1.35 (12H + 12H', m, ^{t}Bu + CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.42 (C), 211.40 (C), 165.9 (C), 165.6 (C), 151.1 (C), 151.0 (C), 138.8 (C), 138.7 (C), 126.2 (CH), 125.9 (CH), 125.6 (CH), 125.5 (CH), 100.4 (CH), 100.2 (CH), 90.8 (CH), 90.7 (CH), 71.3 (CH), 71.2 (CH), 61.2 (CH_2), 61.1 (CH_2), 34.60 (C), 34.58 (C), 31.3 (2 x CH_3), 14.2 (2 x CH_3); Found (FTMS+ p NSI) $[M + Na]^+$ 297.1458, $C_{17}H_{22}O_3Na$ requires 297.1461.

Ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)-5-hydroxypenta-2,3-dienoate (86h)

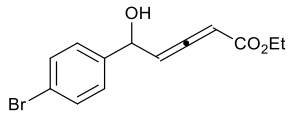


General procedure A was followed but on smaller scale; propargylic alcohol (191.3 mg, 1.09 mmol, 1 equiv.), CuI (10.2 mg, 0.05 mmol, 0.05 equiv.), EDA (0.14 ml, 1.31 mmol, 1.2 equiv.) and MeCN (1.1 ml) to yield product **86h** as a yellow oil and a 1:0.8 mixture of diastereomers (178 mg, 0.68 mmol, 63%). Purified by column chromatography (eluent: hexane/ethyl acetate 3:1).

R_f 0.49 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3400 br (OH), 2982 (C-H), 1961 (C=C, allene), 1709 (C=O), 1502, 1487, 1441 (Ar C-C), 1241 (C-O-C), 1158 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96-6.98 (1H', m, minor, Ar-H), 6.94-6.96 (1H, m, major, Ar-H), 6.89-6.92 (1H', m, minor, Ar-H), 6.86-6.89 (1H, m, major, Ar-H), 6.77 (1H, s, major, Ar-H), 6.75 (1H', s, minor, Ar-H), 5.94 (2H', s, minor, OCH_2O), 5.93 (2H, s, major, OCH_2O),

5.79-5.86 (1H + 1H', m, allene H), 5.71-5.79 (1H + 1H', m, allene H), 5.29-5.35 (1H, m, major, HOC<u>H</u>), 5.23-5.29 (1H', m, minor, HOC<u>H</u>), 4.12-4.24 (2H + 2H', m, OCH_2), 3.25 (1H', d, *J* = 4.2 Hz, minor, OH), 3.19 (1H, d, *J* = 4.3 Hz, major, OH), 1.24-1.33 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.4 (C, major), 211.3 (C, minor), 165.9 (C, minor), 165.6 (C, major), 147.9 (C, minor), 147.8 (C, major), 147.5 (C, minor), 147.3 (C, major), 135.9 (C, major), 135.8 (C, minor), 120.0 (CH, minor), 119.6 (CH, major), 108.11 (CH, minor), 108.07 (CH, major), 107.1 (CH, minor), 106.9 (CH, major), 101.13 (CH_2, minor), 101.10 (CH_2, major), 100.4 (CH, minor), 100.2 (CH, major), 91.0 (CH, minor), 90.7 (CH, major), 71.22 (CH, minor), 71.21 (CH, major), 61.3 (CH_2, minor), 61.2 (CH_2, major), 14.2 (CH_3, major + minor); Found (FTMS+ p NSI) $[M + Na]^+$ 285.0735, $C_{14}H_{14}O_5Na$ requires 285.0733.

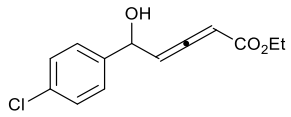
Ethyl 5-(4-bromophenyl)-5-hydroxypenta-2,3-dienoate (86i)



General procedure B was followed to yield product **86i** as an orange solid and a 1:1 mixture of diastereomers (212 mg, 0.71 mmol, 60%). Purified by column chromatography (eluent: hexane/ethyl acetate 3:1).

R_f 0.38 (3:1 hexane/ethyl acetate); Mp 66-71 °C ($CDCl_3$); 3400 br (OH), 2981 (C-H), 1962 (C=C, allene), 1694 (C=O), 1487, 1444 (Ar C-C), 1254 (C-O-C), 1159 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.45-7.51 (2H + 2H', m, Ar-H), 7.32-7.34 (2H', m, Ar-H), 7.28-7.32 (2H, m, Ar-H), 5.80-5.89 (1H + 1H', m, allene H), 5.73-5.78 (1H + 1H', m, allene H), 5.30-5.40 (1H + 1H', m, C<u>H</u>OH), 4.11-4.25 (2H + 2H', m, OCH_2), 3.34 (1H, d, *J* = 4.0 Hz, OH), 3.17 (1H', d, *J* = 4.5 Hz, OH), 1.17-1.41 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.5 (2 x C), 165.8 (C), 165.5 (C), 140.7 (C), 140.6 (C), 131.7 (CH), 131.6 (CH), 128.1 (CH), 127.9 (CH), 122.0 (C), 121.9 (C), 100.1 (CH), 99.8 (CH), 91.0 (CH), 90.9 (CH), 70.90 (CH), 70.86 (CH), 61.4 (CH_2), 61.2 (CH_2), 14.2 (2 x CH_3); Found (FTMS+ p NSI) $[M + Na]^+$ 318.9942, $C_{13}H_{13}O_3BrNa$ requires 318.9940.

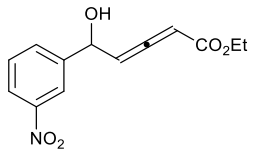
Ethyl 5-(4-chlorophenyl)-5-hydroxypenta-2,3-dienoate (86j)[13]



General procedure B was followed to yield product **86j** as a brown oil and a 1:0.95 mixture of diastereomers (368 mg, 1.46 mmol, 94%).

R_f 0.33 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3400 br (OH), 2982 (C-H), 1962 (C=C, allene), 1712 (C=O), 1594, 1490, 1444 (Ar C-C), 1255 (C-O-C), 1159 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.40 (4H + 4H', m, Ar-H), 5.79 (1H + 1H', m, allene H), 5.83 (1H + 1H', m, allene H), 5.71-5.77 (1H + 1H', m, C<u>H</u>OH), 4.14-4.24 (2H + 2H', m, OCH_2), 3.50 (1H, bs, major, OH), 3.31 (1H', bs, minor, OH), 1.25-1.31 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 211.5 (C), 211.4 (C), 165.8 (C), 165.4 (C), 140.2 (C), 140.1 (C), 133.9 (C), 133.7 (C), 128.7 (CH), 128.6 (CH), 127.8 (CH), 127.5 (CH), 100.2 (CH), 100.0 (CH), 90.9 (CH), 90.8 (CH), 70.8 (2 x CH), 61.3 (CH_2), 61.2 (CH_2), 14.2 (2 x CH_3).

Ethyl 5-hydroxy-5-(3-nitrophenyl)penta-2,3-dienoate (86k)[13]

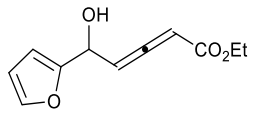


General procedure A was followed to obtain product **86k** as a yellow oil and a 1:0.7 mixture of diastereomers (11.8 mg, 0.04 mmol, 6%). Purified by column chromatography (eluent: hexane/ethyl acetate 3:1)

R_f 0.17 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3422 br (OH), 2983 (C-H) 1963 (C=C, allene), 1713 (C=O), 1510 (NO_2), 1583, 1476, 1444 (Ar C-C), 1340 (NO_2), 1255 (C-O-C), 1178 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (1H, 8.42, br t, *J* = 1.7 Hz, Ar-H), 8.31 (1H, dt, *J* = 12.7, 1.7 Hz, Ar-H), 8.11-8.20 (2H, m, Ar-H), 7.85-7.91 (1H, m, Ar-H), 7.75-7.83 (1H, m, Ar-H), 7.52 (2H, q, *J* = 7.7 Hz, Ar-H), 5.84-5.91 (1H, m, minor, HOCHC<u>H</u>=C=CH), 5.77 (1H, td, *J* = 1.9 Hz, 6.0 Hz, major, HOCHC<u>H</u>=C=CH), 5.54-5.61 (1H, m, minor, CH=C=C<u>H</u>CO_2Et), 5.51 (1H, m, major, CH=C=C<u>H</u>CO_2Et), 4.15-4.25 (2H, m, major, OCH_2), 4.02-4.13 (2H, m, minor, OCH_2), 3.78 (1H, br s, minor, OH), 3.70 (1H, br s, major, OH), 1.20-1.33 (6H, m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 211.6 (C, major + minor), 165.4 (C, minor), 165.2 (C, major), 148.4 (C, major + minor),

143.7 (C, major), 143.6 (C, minor), 132.4 (CH, minor), 132.3 (CH, major), 129.6 (CH, minor), 129.5 (CH, major), 123.1 (CH, minor), 123.0 (CH, major), 121.4 (CH, minor), 121.2 (CH, major), 99.7 (CH, minor), 99.3 (CH, major), 91.4 (CH, minor), 91.2 (CH, major), 70.8, (CH, major), 70.6 (CH, minor), 61.5 (CH_2, minor), 61.4 (CH_2, major), 14.2 (CH_3, major + minor).

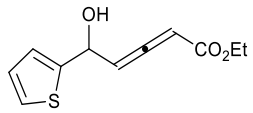
Ethyl 5-(furan-2-yl)-5-hydroxypenta-2,3-dienoate (86l)[13]



General procedure B was followed to yield product **86l** as a yellow oil and a 1:1 mixture of diastereomers (299 mg, 1.44 mmol, 71%). Purified by column chromatography (eluent: hexane/ethyl acetate 3:1).

R_f 0.31 (3:1 hexane/ethyl acetate); 3399 br (OH), 2983 (C-H), 1964 (C=C, allene), 1711 (C=O), 1502, 1445, 1414 (Ar C-C), 1255 (C-O-C), 1159 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.37 (1H + 1H', m, furan-H), 6.28-6.36 (2H + 2H', m, furan-H), 5.88-5.99 (1H + 1H', m, HOCHC<u>H</u>=C=CH), 5.75 (1H, dd, *J* = 3.5, 2.4 Hz, HOCHCH=C=C<u>H</u>), 5.73 (1H', dd, *J* = 3.5, 2.5 Hz, HOCHCH=C=C<u>H</u>), 5.38 (1H, td, *J* = 5.8, 2.4 Hz, HOC<u>H</u>), 5.33 (1H', m, HOC<u>H</u>), 4.10-4.20 (2H + 2H', m, OCH_2), 3.97 (1H', d, *J* = 5.4 Hz, OH), 3.90 (1H, d, *J* = 5.7 Hz, OH), 1.19-1.29 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.0 (C), 211.7 (C), 165.9 (C), 165.6 (C), 154.10 (C), 154.08 (C), 142.51 (CH), 142.49 (CH), 110.34 (CH), 110.32 (CH), 107.2 (CH), 107.1 (CH), 97.7 (CH), 97.6 (CH), 91.1 (CH), 90.9 (CH), 65.1 (CH), 64.9 (CH), 61.3 (CH_2), 61.2 (CH_2), 14.1 (CH_3 x 2).

Ethyl 5-hydroxy-5-(thiophen-2-yl)penta-2,3-dienoate (86m)

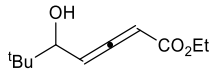


General procedure A was followed to yield product **86m** as a yellow oil and a 1:1.2 mixture of diastereomers (71 mg, 0.32 mmol, 16%). Purified by column chromatography (eluent: hexane/ethyl acetate 4:1).

R_f 0.40 (3:1 hexane/ethyl acetate); 3400 br (OH), 2981 (C-H), 1962 (C=C, allene), 1710 (C=O), 1517, 1445, 1414 (Ar C-C), 1254 (C-O-C), 1159 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.30 (1H', m, thiophene-H, minor), 7.25-7.27 (1H, m, thiophene-H, major),

7.07-7.11 (1H + 1H', m, thiophene-H), 6.96-7.02 (1H + 1H', m, thiophene-H), 5.94-6.00 (1H + 1H', m, allene H), 5.77-5.82 (1H + 1H, m, allene H), 5.57-5.67 (1H + 1H', m, C<u>H</u>OH), 4.41-4.25 (2H + 2H', m, OCH_2), 3.26 (1H', d, *J* = 4.9 Hz, OH, minor), 3.15 (1H, d, *J* = 5.2 Hz, OH, major), 1.24-1.33 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.5 (C, minor), 211.3 (C, major), 165.7 (C, minor), 165.4 (C, major), 145.7 (C, major), 145.5 (C, minor), 126.82 (CH, major), 126.80 (CH, minor), 126.8 (CH, minor), 125.6 (CH, major), 124.9 (CH, minor), 124.8 (CH, major), 100.0 (CH, minor), 99.8 (CH, major), 91.31 (CH, major), 91.29 (CH, minor), 67.6 (CH, major), 67.4 (CH, minor), 61.3 (CH_2, minor), 61.2 (CH_2, major), 14.2 (CH_3, major + minor); Found (FTMS+ p NSI) $[M + Na]^+$ 247.0401, $C_{11}H_{12}O_3SNa$ requires 247.0399.

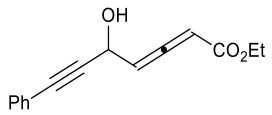
Ethyl 5- hydroxy-6,6-dimethylhepta-2,3-dienoate (86n)



General procedure A was followed to yield product **86n** as a pale yellow liquid and a 1:1.2 mixture of diastereomers (360 mg, 1.81 mmol, 72%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1 to 5:1).

R_f 0.67 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3434 br (OH), 2955, 2906 (C-H), 1960 (C=C, allene), 1715 (C=O), 1252 (C-O-C), 1157 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 5.61-5.75 (2H + 2H', m, allene H), 4.06-4.21 (2H + 2H', m, OCH_2), 3.87-4.00 (1H +1H', m, C<u>H</u>OH), 2.80-2.87 (1H', m, OH, minor), 2.69-2.78 (1H, m, OH, major), 1.19-1.28 (3H + 3H', m, CH_3), 0.94 (9H, s, ^{t}Bu, major), 0.93 (9H, s, ^{t}Bu, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.53 (C, major), 211.48 (C, minor), 166.3 (C, minor), 166.0 (C, major), 97.4 (CH, minor), 96.8 (CH, major), 89.7 (CH, minor), 89.2 (CH, major), 77.3 (CH, minor), 77.2 (CH, major), 61.1 (CH_2, minor), 61.0 (CH_2, major), 35.6 (C, minor), 35.5 (C, major), 25.4 (CH_3, major + minor), 14.2 (CH_3, major + minor); Found (FTMS+ p NSI) $[M + Na]^+$ 221.1148, $C_{11}H_{18}O_3Na$ requires 221.1148.

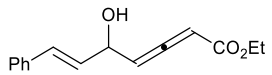
Ethyl 5-hydroxy-7-phenylhepta-2,3-dien-6-ynoate (86o)[13]



General procedure B was followed to yield product **86o** as a yellow oil and a 1:1 mixture of diastereomers (316 mg, 1.30 mmol, 82%). Purified by column chromatography (eluent: hexane/ethyl acetate 3:1).

R_f 0.36 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3399 br (OH), 2981 (C-H), 2232 (C≡C), 1965 (C=C, allene), 1713 (C=O), 1597, 1489, 1443 (Ar C-C), 1255 (C-O-C), 1157 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38-7.44 (2H + 2H', m, Ar-H), 7.26-7.36 (3H + 3H', m, Ar-H), 5.93-5.96 (1H + 1H', m, allene H), 5.81-5.87 (1H + 1H', m, allene H), 5.24-5.32 (1H + 1H', m, C<u>H</u>OH), 4.19 (2H', q, *J* = 7.1 Hz, OCH_2), 4.18 (2H, q, *J* = 7.1 Hz, OCH_2), 3.80-3.91 (1H + 1H', m, OH), 1.26 (3H', t, *J* = 7.1 Hz, CH_3), 1.25 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.9 (C), 211.8 (C), 165.6 (C), 165.5 (C), 131.8 (2 x CH), 128.7 (2 x CH), 128.3 (2 x CH), 122.2 (2 x C), 98.5 (CH), 98.4 (CH), 91.7 (CH), 91.3 (CH), 87.2 (2 x C), 86.0 (C), 85.9 (C), 61.4 (CH_2), 61.3 (CH_2), 60.3 (CH), 60.0 (CH), 14.2 (2 x CH_3).

(*E*)-Ethyl 5-hydroxy-7-phenylhepta-2,3,6-trienoate (86p)[13]

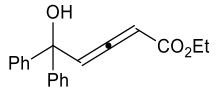


General procedure B was followed to yield product **86p** as a yellow oil and a 1:1 mixture of diastereomers (388 mg, 1.59 mmol, 84%). Purified by column chromatography (eluent: hexane/ethyl acetate 4:1).

R_f 0.40 (4:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3399 br (OH), 2981 (C-H), 1960 (C=C, allene), 1711 (C=O), 1494, 1447, 1414 (Ar C-C), 1253 (C-O-C), 1156 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20-7.40 (5H + 5H', m, Ar-H), 6.68-6.72 (1H', m, PhCH=C<u>H</u>), 6.63-6.67 (1H, m, PhCH=C<u>H</u>), 6.28 (1H, d, *J* = 15.9 Hz, PhC<u>H</u>=CH), 6.26 (1H', d, *J* = 15.9 Hz, PhC<u>H</u>=CH), 5.79-5.87 (1H + 1H', m, allene H), 5.74-5.79 (1H + 1H', m, allene H), 4.96-5.06 (1H + 1H', m, C<u>H</u>OH), 4.13-4.23 (2H + 2H', m, OCH_2), 3.60 (1H', d, *J* = 4.6 Hz, OH), 3.47 (1H, d, *J* = 5.0 Hz, OH), 1.21-130 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 211.7 (C), 211.4 (C), 165.9 (C), 165.8 (C), 136.3 (2 x C), 131.40 (CH), 131.38 (CH), 129.37 (CH), 129.32 (CH), 128.6 (2 x CH), 128.0 (2 x CH), 126.7 (2 x CH),

99.3 (CH), 99.2 (CH), 91.0 (CH), 90.5 (CH), 70.0 (CH), 69.8 (CH), 61.3 (CH_2), 61.2 (CH_2), 14.2 (2 x CH_3).

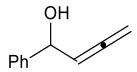
Ethyl 5-hydroxy-5,5-diphenylpenta-2,3-dienoate (86q)



General procedure A was followed to yield product **86q** as a yellow oil (340 mg, 1.16 mmol, 97%). Purified by column chromatography (eluent: hexane/ethyl acetate 15:1 to 10:1 to 5:1).

R_f 0.34 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3433 br (OH), 2981 (C-H), 1963 (C=C, allene), 1697 (C=O), 1492, 1447, 1410 (Ar C-C), 1261 (C-O-C), 1162 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.52 (2H, m, Ar-H), 7.44-7.47 (2H, m, Ar-H), 7.27-7.37 (6H, m, Ar-H), 6.31 (1H, d, *J* = 6.1 Hz, allene-H), 5.70 (1H, d, *J* = 6.1 Hz, allene-H), 4.14-2.24 (2H, m, OCH_2), 2.86 (1H, s, OH), 1.31 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 211.0 (C), 165.4 (C), 145.0 (C), 144.9 (C), 128.24 (CH), 128.15 (CH), 127.8 (CH), 127.7 (CH), 126.8 (CH), 126.5 (CH), 104.9 (CH), 92.1 (CH), 78.4 (C), 61.1 (CH_2), 14.2 (CH_3); Found (FTMS+ p NSI) $[M + NH_4]^+$ 312.1597, $C_{19}H_{22}O_3N$ requires 312.1594.

1-Phenylbuta-2,3-dien-1-ol (73b)[37]

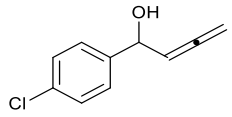


To a round bottomed flask, propargylic alcohol (348 mg, 2.63 mmol, 1 equiv.), paraformaldehyde (157 mg, 5.22 mmol, 2 equiv.), CuI (305 mg, 1.60 mmol, 0.6 equiv.), diisopropyl amine (0.73 ml, 5.26 mmol, 2 equiv.) and dry dioxane (8.8 ml, 0.30 M) were added. The reaction was stirred at 115 ^oC for 18 h. The reaction mixture was then cooled and filtered through a plug of silica (eluent: hexane/ethyl acetate 4:1, 200 ml). The solvent was then removed on a rotary evaporator. Purified by column chromatography (eluent: hexane/ethyl acetate, 4:1) to yield product **73b** as a yellow oil (266 mg, 1.82 mmol, 76%).

R_f 0.32 (10:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3338 br (OH), 3029 (C-H) 1953 (C=C, allene); ^{1}H NMR (300 MHz, $CDCl_3$), δ 7.27-7.43 (5H, m, Ar-H), 5.45 (1H, q, *J* = 6.5 Hz, C<u>H</u>=C=CH_2), 5.23-5.31 (1H, m, C<u>H</u>OH), 4.90-4.96 (2H, m, CH=C=C<u>H</u>$_2$), 2.44 (1H, bs,

OH); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 207.1 (C), 142.7 (C), 128.5 (CH), 127.7 (CH), 126.1 (CH), 95.2 (CH), 78.2 (CH_2), 71.9 (CH).

1-(4-Chlorophenyl)-buta-2,3-diene-1-ol (73j)[21]

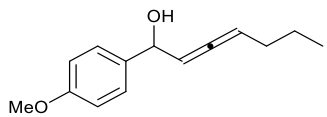


Dioxane was dried by refluxing over CaH for 2 hours and then distilled into molecular sieves before use.

To a dry round bottom flask, proparyglic alcohol (191.1 mg, 1.15 mmol, 1.0 equiv.), CuI (112.4 mg, 0.59 mmol, 0.5 equiv.), paraformaldehyde (84.9 mg, 2.83 mmol, 2.5 equiv.) were dissolved in dioxane (1.7 ml). Diisopropyl amine (0.3 ml, 2.07 mmol, 1.8 equiv.) was added and the mixture was refluxed for 2 hours under argon. The reaction mixture was then allowed to cool to room temperature and filtered (washed with diethyl ether). Water (10 ml) was added and the product was extracted with diethyl ether. The organic layer was then dried with $MgSO_4$, filtered and the solvent removed using a rotary evaporator. Purified by column chromatography (eluent 5:1 hexane/ethyl acetate) to yield product **73j** as a yellow liquid (60.1 mg, 0.33 mmol, 29%).

R_f 0.50 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3333 (OH), 2886 (C-H), 1954 (C=C, allene), 1490, 1406, 1344 (Ar C-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (4H, s, Ar-H), 5.36-5.45 (1H, m, HOC<u>H</u>), 5.23-5.29 (1H, m, CH=C), 4.95-4.92 (2H, m, C=C<u>H</u>$_2$), 2.17 (1H, d, *J* = 4.0 Hz, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.2 (C), 141.3 (C), 133.5 (C), 128.7 (CH), 128.6 (CH), 95.0 (CH), 78.5 (CH_2), 71.3 (CH).

1-(4-Methoxyphenyl)hepta-2,3-dien-1-ol (73e)[21]



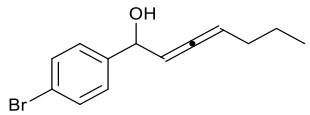
Dioxane was dried over CaH by refluxing for 2 hours then distilled into molecular sieves before use. Butraldehyde was freshly distilled before use. Dibutylamine was distilled over CaH before use.

To a round bottomed flask, propargylic alcohol (190.0 mg, 1.17 mmol, 1 equiv.), butraldehyde (0.17 ml, 1.87 mmol, 1.6 equiv.), CuI (25.5 mg, 0.10 mmol, 10 mol%),

dibutylamine (0.28 ml, 1.64 mmol, 1.4 equiv.) and dry dioxane (3.8 ml, 0.34 M) were added. The reaction was stirred at 130 °C for 18 h. The solvent was then removed on a rotary evaporator. Purified by column chromatography (eluent: hexane/ethyl acetate, 10:1) to yield product **73e** as a yellow liquid and a 1:1 mixture of diastereomers (74.8 mg, 0.34 mmol, 29%).

R_f 0.24 (10:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3383 (OH), 2956, 2931, 2871 (C-H), 1961 (C=C, allene), 1463, 1444 (Ar C-C), 1246 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.9 Hz, Ar-H), 6.89 (2H, d, *J* = 8.9 Hz, Ar-H), 5.33-5.44 (2H, m, allene-H), 5.16-5.21 (1H, m, HOC<u>H</u>), 3.81 (3H, s, OMe), 2.07-2.10 (1H, m, OH), 1.98-2.07 (2H, m, C=CHC<u>H$_2$</u>), 1.38-1.51 (2H, m, $CH_2C\underline{H_2}CH_3$), 0.87-0.97 (3H, m, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) 202.3 (C), 202.1 (C), 159.21 (C), 159.17 (C), 135.5 (C), 135.4 (C), 127.5 (CH), 127.4 (CH), 113.9 (CH), 113.8 (CH), 96.22 (CH), 96.15 (CH), 95.0 (CH), 94.7 (CH), 72.0 (CH), 71.8 (CH), 55.3 (2 x CH_3), 30.9 (CH_2), 30.8 (CH_2), 22.33 (CH_2), 22.30 (CH_2), 13.63 (CH_3), 13.61 (CH_3).

1-(4-Bromophenyl)hepta-2,3-dien-1-ol (73i)



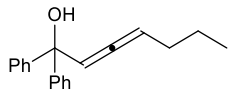
Dioxane was dried over CaH by refluxing for 2 hours then distilled into molecular sieves before use. Butraldehyde was freshly distilled before use. Dibutylamine was distilled over CaH before use.

To a round bottomed flask, propargylic alcohol (207 mg, 0.98 mmol, 1 equiv.), butraldehyde (0.14 ml, 1.57 mmol, 1.6 equiv.), CuI (36.2 mg, 0.10 mmol, 10 mol%), dibutylamine (0.23 ml, 1.37 mmol, 1.4 equiv.) and dry dioxane (2.8 ml, 0.34 M) were added. The reaction was stirred at 130 °C for 18 h. The solvent was then removed on a rotary evaporator. Purified by column chromatography (eluent: hexane/ethyl acetate, 10:1 to5:1) to yield product **73i** as a yellow liquid and a 1:1 mixture of diastereomers (164.4 mg, 0.62 mmol, 62%).

R_f 0.24 (10:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3334 (OH), 2957, 2928, 2870 (C-H), 1961 (C=C, allene), 1485, 1455, 1398 (Ar C-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (2H, d, *J* = 8.6 Hz, Ar-H), 7.27 (2H, d, *J* = 8.6 Hz, Ar-H), 5.34-5.39 (2H, m, allene-H), 5.16-5.21 (1H, m, HOC<u>H</u>), 2.16 (1H, br t, *J* = 2.6 Hz, OH), 1.97-2.05 (2H, m, C=CHC<u>H$_2$</u>), 1.42

(2H, sext, *J* = 7.4 Hz, $CH_2C\underline{H_2}CH_3$), 0.88-0.97 (3H, m, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) 202.5 (C), 202.3 (C), 142.2 (C), 142.1 (C), 137.5 (CH), 131.5 (CH), 128.1 (CH), 127.9 (CH), 121.46 (C), 121.43 (C), 95.84 (CH), 95.76 (CH), 95.4 (CH), 95.1 (CH), 71.8 (CH), 71.6 (CH), 30.8 (CH_2), 30.7 (CH_2), 22.28 (CH_2), 22.26 (CH_2), 13.6 (2 x CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 267.0375, $C_{13}H_{16}BrO$ requires 267.0379.

1,1-Diphenylhepta-2,3-dien-1-ol (73q)[21]



Dioxane was dried over CaH by refluxing for 2 hours then distilled into molecular sieves before use. Butraldehyde was freshly distilled before use. Dibutylamine was distilled over CaH before use.

To a round bottomed flask, propargylic alcohol (206.5 mg, 0.99 mmol, 1 equiv.), butraldehyde (0.14 ml, 1.58 mmol, 1.6 equiv.), CuI (39.4 mg, 20 mol%), dibutylamine (0.24 ml, 1.39 mmol, 1.4 equiv.) and dry dioxane (3.0 ml, 0.34 M) were added. The reaction was stirred at 150 ^oC for 26 h. The solvent was then removed on a rotary evaporator. Purified by column chromatography (eluent: hexane/ethyl acetate, 20:1 to 10:1) to yield product **73q** as a yellow liquid (50 mg, 0.19 mmol, 19%).

R_f 0.38 (10:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3455 (OH), 3059, 3025, 2958, 2930, 2871 (C-H), 1962 (C=C, allene), 1491, 1447 (Ar C-C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.46 (4H, m, Ar-H), 7.29-7.35 (4H, m, Ar-H), 7.24-7.27 (2H, m, Ar-H), 5.91 (1H, dt, *J* = 6.2, 2.9 Hz, $C=C\underline{H}CH_2$), 5.41 (1H, q, *J* = 6.2 Hz, $C\underline{H}=C$), 2.66 (1H, s, OH), 1.96-2.04 (2H, m, $CHC\underline{H_2}$), 1.38 (2H, sext, *J* = 7.4 Hz, $CH_2C\underline{H_2}CH_3$), 0.87 (3H, t, *J* = 7.4 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 200.9 (C), 146.42 (C), 146.40 (C), 128.01 (CH), 127.99 (CH), 127.1 (CH), 126.8 (CH), 126.7 (CH), 126.7 (CH), 100.9 (CH), 97.1 (CH), 77.2 (C), 30.9 (CH_2), 22.7 (CH_2), 13.6 (CH_3).

Preparation of 1,3-Dienes

General procedure C: Using Au(I) Catalysis

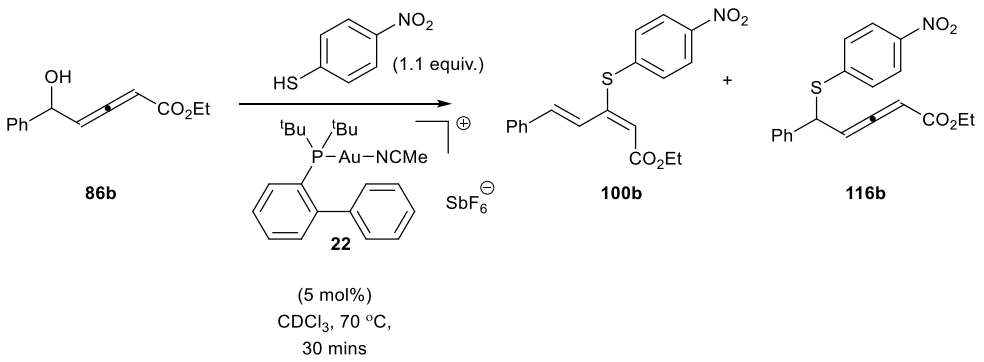
Allenol (0.070 mmol, 1 equiv.) was added to a sealed tube and dissolved in $CDCl_3$ (0.35 ml). Au(I) catalyst (5 mol%) and thiol (0.077 mmol, 1.1 equiv.) were dissolved in $CDCl_3$ (0.15 ml) and added to the sealed tube. The vial containing thiol and catalyst (**22**) was washed with $CDCl_3$ (0.2 ml) and the washings added to the sealed tube. The reaction mixture was stirred for 30 minutes and cooled to room temperature. The product was purified by column chromatography (hexane/ethyl acetate).

General procedure D: Using $InCl_3$ Catalysis

Allenol (0.105 mmol, 1.5 equiv.) was dissolved in a $CHCl_3$ (0.15 ml). $InCl_3$ (5 mol%) and thiol (0.07 mmol, 1 equiv.) were added to a CEM microwave tube and dissolved in $CHCl_3$ (0.35 ml). The allenol solution was added and the vial washed with additional $CHCl_3$ (0.2 ml) into the microwave tube. The tube was placed in the microwave and heated at 70 °C, 300 W, for 10 minutes. The mixture was allowed to cool before it was passed through a plug of silica and washed with ether. The filtrate was then concentrated on a rotary evaporator. The products was purified by column chromatography (hexane/ethyl acetate).

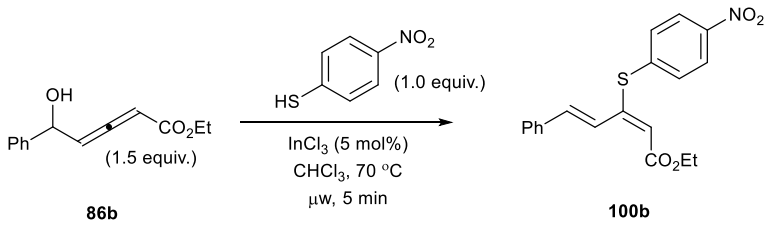
E,*E* Stereochemistry for **100b** confirmed by X-ray structure and NOE where possible. The *E*,*E* stereochemistry for the others are assigned by analogy with the rest in the series.

(2*E*, 4*E*)-Ethyl 3-(4-nitrophenylthio)-5-phenylpenta-2,4-dienoate (100b)



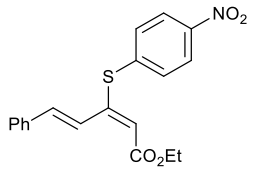
General procedure A: using Au(I) catalysis

General procedure C was followed to yield title product **100b** as a yellow solid (6.3 mg, 0.02 mmol, 25%) and product **116b** as a yellow oil (7.5 mg, 0.02 mmol, 30%). Purified by column chromatography (eluent: hexane/ethyl acetate, 80:1 to 70:1 to 50:1 to 25:1).



General procedure B: using $InCl_3$ catalysis

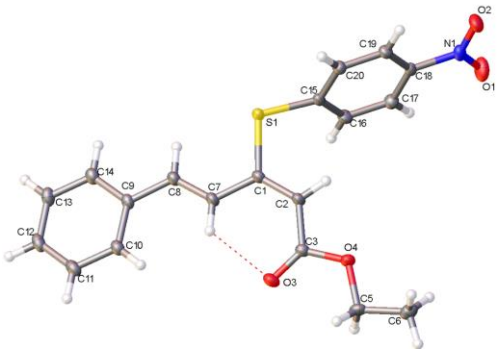
General procedure D was followed to yield title product **100b** as a yellow solid (12 mg, 0.03 mmol, 49%). Purified by column chromatography (eluent: hexane/ethyl acetate, 80:1 to 70:1 to 50:1 to 25:1).



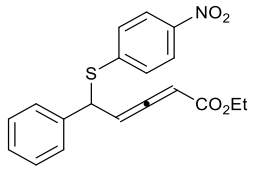
R_f 0.66 (5:1 hexane/ethyl acetate); Mp 111-113 °C ($CDCl_3$); ν_{max}/cm^{-1} 3097 (C-H), 2098 (C-H), 1703 (C=O), 1614 (C=C, diene conj), 1597 (C=C, diene conj), 1576, 1561 (Ar C-C), 1518 (NO_2), 1340 (NO_2), 1192 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.35 (1H, dd, *J* = 15.9 Hz, 0.8 Hz, PhCH=C<u>H</u>), 8.18 (2H, d, *J* = 8.9 Hz, Ar-H), 7.54 (2H, d, *J* = 8.9 Hz, Ar-H), 7.47-7.52 (2H, m, Ar-H), 7.28-7.41 (4H, m, Ar-H + PhC<u>H</u>=CH), 5.95 (1H, app. s, SC=C<u>H</u>), 4.21 (2H, q, *J* = 7.1 Hz, OCH_2), 1.30 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), 164.8 (C), 149.9 (C), 146.8 (C), 142.7 (C), 138.9 (CH), 135.7 (C), 131.0 (CH), 129.5 (CH), 128.8 (CH), 127.8 (CH), 124.4 (CH), 123.3 (CH), 121.1 (CH), 60.6 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 356.0950, $C_{19}H_{18}NO_4S$ requires 356.0951.

Crystals grown by vapour diffusion from $CHCl_3$-hexane: Crystal data: $C_{19}H_{17}NO_4S$, *M* = 355.40, triclinic, *a* = 9.6997(7), *b* = 9.9793(6), *c* = 10.2055(7), *β* = 73.565(4)°, *U* = 869.20(10) Å^3, *T* = 100 K, space group P-1, *Z* = 2, μ(MoKα) = 0.210 mm^{-1}, 26793 reflections measured, 7525 independent reflections (R_{int} = 0.0465). The final *w*R_2 was 0.1146.

E, *E* stereochemistry confirmed by crystal structure:-

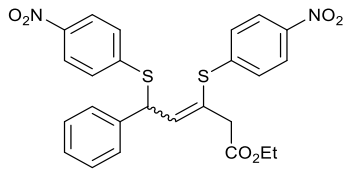


Ethyl 5-(4-nitrophenylthio)-5-phenylpenta-2,3-dienoate (116b)



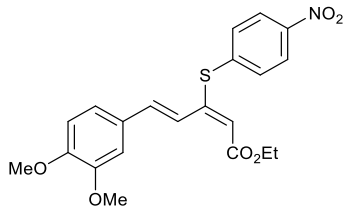
R_f 0.58 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1}, 2979 (C-H), 1980 (C=C, allene), 1698 (C=O), 1613, 1596, 1575, (Ar C-C), 1513 (NO_2), 1336 (NO_2) 1215 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), dr 1:1.4, δ 8.19 (2H + 2H', d, *J* = 9.1 Hz, major + minor, Ar-H), 8.11 (1H + 1H', m, Ar-H), 7.62 (2H +2H', d, *J* = 9.1 Hz, Ar-H), 7.28-7.48 (4H + 4H', m, Ar-H), 6.04 (1H, dd, *J* = 7.4, 6.1 Hz, major, SCHC<u>H</u>=C=CH), 5.99 (1H', dd, *J* = 7.3, 6.1 Hz, minor, SCHC<u>H</u>=C=CH), 5.71 (1H, dd, *J* = 6.1, 2.2, Hz, major, SCHCH=C=C<u>H</u>), 5.66 (1H, dd, *J* = 6.1, 2.3 Hz, minor, SCHCH=C=C<u>H</u>), 5.15 (1H, dd, *J* = 7.3, 2.3 Hz, minor, SC<u>H</u>CH=C=CH), 5.13 (1H, dd, *J* = Hz, 7.3, 2.2 Hz, major, SC<u>H</u>CH=C=CH), 4.16 (2H + 2H', q, *J* = 7.1 Hz, OCH_2), 1.26 (3H + 3H', t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ 212.6 (C, minor), 212.4 (C, major), 164.8 (C, major), 164.7 (C, minor), 147.0 (C, major), 145.3 (C, major), 145.0 (C, minor), 144.1 (C, major), 137.8 (C, major), 137.7 (C, minor), 129.0 (CH, major), 128.9 (CH, minor), 128.5 (CH, major + minor), 127.9 (CH, major), 127.8 (CH, minor), 126.4 (CH, minor), 124.4 (CH, major), 123.9 (CH, major), 123.8 (CH, minor), 97.3 (CH, major, SCH<u>C</u>H=C=CH, confirmed by HSQC), 97.1 (CH, minor, SCH<u>C</u>H=C=CH, confirmed by HSQC), 91.6 (CH, major, SCHCH=C=<u>C</u>H, confirmed by HSQC), 91.3 (CH, minor, SCHCH=C=<u>C</u>H, confirmed by HSQC), 61.2 (CH_2, major), 61.1 (CH_2, minor), 49.9 (CH, minor, S<u>C</u>HCH=C=CH, confirmed by HSQC), 49.4 (CH, major, , S<u>C</u>HCH=C=CH, confirmed by HSQC), 14.2 (CH_3, major), 14.1 (CH_3, minor); Found (FTMS+ p APCI) $[M + H]^+$ 356.0950, $C_{19}H_{18}NO_4S$ requires 356.0951. This product decomposes in <1 month.

(*Z*)-Ethyl 3,5-bis(4-nitrophenylthio)-5-phenylpent-3-encate (117b)



ν_{max}/cm^{-1}, 2923 (C-H), 1731 (C=O), 1513 (NO_2), 1595, 1576, 1476, (Ar C-C), 1336 (NO_2) 1180 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), *E*/*Z* 1:0.3, δ 8.07 (2H + 2H', d, *J* = 8.9 Hz, Ar-H), 8.03 (2H + 2H', d, *J* = 8.0 Hz, Ar-H), 7.48 (2H + 2H', d, *J* = 9.0 Hz, Ar-H) 7.27-7.44 (5H + 5H', m, Ar-H), 7.20 (2H + 2H', d, *J* = 9.0 Hz, Ar-H), 6.56 (1H, d, *J* = 10 Hz, major, C<u>H</u>=CS), 6.47 (1H', d, *J* = 9.8 Hz, minor, C<u>H</u>=CS), 5.66 (1H, d, *J* = 9.9 Hz, major, SC<u>H</u>-CH=CS), 5.35 (1H', d, *J* = 9.8 Hz, minor, SC<u>H</u>-CH=CS), 4.10 (2H + 2H', q, *J* = 7.1 Hz, OCH_2), 3.26 (2H + 2H', s, C<u>H</u>$_2$$CO_2Et$), 1.17 (3H + 3H', m, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), δ 169.3 (C, major), 168.8 (C, minor), 146.4 (C, major), 146.2 (C, minor), 146.2 (C, minor), 144.1 (C, major), 143.2 (C, minor), 142.1 (CH, major + minor), 138.9 (C, minor), 137.7 (C, major), 130.4 (CH, major + minor), 129.1 (CH, major + minor), 128.4 (CH, minor), 128.3 (CH, major), 127.8 (CH, minor), 127.7 (CH, major), 126.8 (C, major + minor), 126.4 (CH, major + minor), 124.4 (CH, major + minor), 124.2 (CH, minor), 124.1 (CH, major), 123.9 (CH, major + minor), 65.8 (CH_2, minor), 61.3 (CH_2, major), 51.7 (CH, major), 50.8 (CH, minor), 43.0 (CH_2, major), 38.2 (CH_2, minor), 15.3 (CH_3, minor), 14.1 (CH_3, major); Found (FTMS + p APCI) $[M + H]^+$ 528.1251, $C_{25}H_{26}N_3O_6S_2$ requires 528.1258.

(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100c)

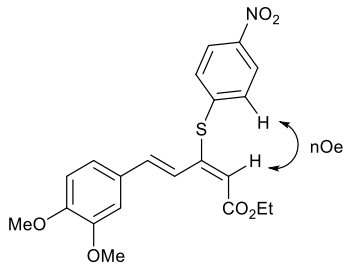


General procedure D was followed to obtain product **100c** as yellow oil (23.3 mg, 0.06 mmol, 80%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

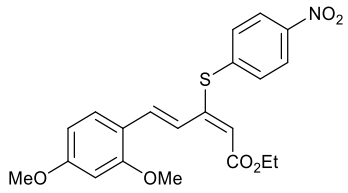
R_f 0.25 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2935 (C-H alkyl), 1699 (C=O), 1596 (C=C diene), 1578, 1557 (Ar C-C), 1510 (NO_2), 1367 (NO_2), 1177 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (1H, dd, *J* = 15.8, 0.8 Hz, CH=C<u>H</u>CS), 8.17 (2H, d, *J* = 9.0 Hz, Ar-

H), 7.52 (2H, d, *J* = 9.0 Hz, Ar-H), 7.29 (1H, d, *J* = 15.8 Hz, C<u>H</u>=CHCS), 7.06 (2H, m, Ar-H), 6.82 (1H, m, Ar-H), 5.92 (1H, app. t, *J* = 0.6 Hz, SC=C<u>H</u>), 4.21 (2H, q, *J* = 7.1 Hz, OCH_2), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 1.30 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.0 (C), 150.6 (C), 149.9 (C), 149.2 (C), 146.7 (C), 143.2 (C), 139.1 (CH), 130.7 (CH), 128.8 (C), 124.4 (CH), 122.1 (CH), 121.4 (CH), 120.4 (CH), 111.1 (CH), 109.7 (CH), 60.5 (CH_2), 55.97 (CH_3), 55.95 (CH_3), 14.2 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 416.1169, $C_{21}H_{22}NO_6S$ requires 416.1162.

E, *E* stereochemistry confirmed by NOESY δ 5.92 and 7.52.



(2*E*, 4*E*)-Ethyl 5-(2,4-dimethoxyphenyl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100d)

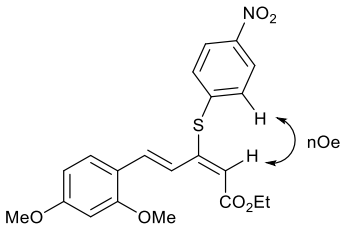


General procedure D was followed to yield product **100d** as a yellow solid (27.9 mg, 0.07 mmol, 96%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

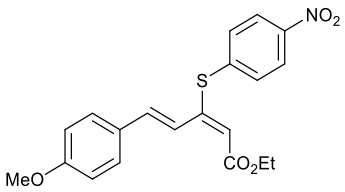
R_f 0.36 (5:1 hexane/ethyl acetate); Mp: 126-128 °C ($CDCl_3$); ν_{max}/cm^{-1} 2938 (C-H), 1698 (C=O), 1596 (C=C, diene conj), 1515 (NO_2), 1556, 1463, 1438, 1419 (Ar C-C), 1337 (NO_2), 1159 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.28 (1H, dd, *J* = 16.0, 0.8 Hz, CH=C<u>H</u>CS), 8.15 (2H, d, *J* = 9.0 Hz, Ar-H), 7.67 (1H, d, *J* = 16.0 Hz, C<u>H</u>=CHCS), 7.52 (3H, d, *J* = 9.0 Hz, Ar-H), 6.38-6.51 (2H, m, Ar-H), 5.89 (1H, app. s, SC=C<u>H</u>), 4.21 (2H, q, *J* = 7.1 Hz, OCH_2), 3.82 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 1.29 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.1 (C), 162.3 (C), 159.2 (C), 151.1 (C), 146.7 (C), 143.5 (C), 134.2 (CH), 131.0 (CH), 129.0 (CH), 124.5 (CH), 121.2 (CH), 119.3 (CH),

117.9 (C), 105.4 (CH), 98.4 (CH), 60.3 (CH_2), 55.6 (CH_3), 55.5 (CH_3), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 416.1161, $C_{21}H_{22}NO_6S$ requires 416.1162.

E, *E* stereochemistry confirmed by NOESY δ 7.52 and 5.89:



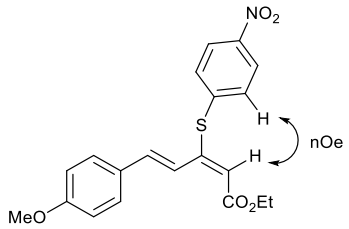
(2*E*, 4*E*)-Ethyl 5-(4-methoxyphenyl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100e)



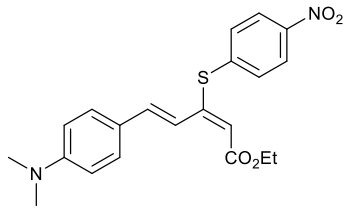
General procedure D was followed with the exception of the microwave conditions – reaction placed in microwave at 90 °C for 20 min to yield product **100e** as a yellow solid (26.3 mg, 0.068 mmol, 79%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1).

R_f 0.51 (5:1 hexane/ethyl acetate); Mp 80-82 °C ($CDCl_3$); ν_{max}/cm^{-1} 3096 (C-H), 2979 (C-H), 1699 (C=O), 1596 (C=C, diene conj), 1509 (NO_2), 1558, 1476, 1463, 1442 (Ar C-C), 1337 (NO_2), 1184 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.26 (1H, dd, *J* = 15.8, 0.9 Hz, CH=C<u>H</u>CS), 8.16 (2H, d, *J* = 9.0 Hz, Ar-H), 7.52 (2H, d, *J* = 9.0 Hz, Ar-H), 7.46 (2H, d, *J* = 8.4 Hz, Ar-H), 7.30 (1H, d, *J* = 15.8 Hz, C<u>H</u>=CHCS), 6.87 (2H, d, *J* = 8.4 Hz, Ar-H), 5.92 (1H, app. t, *J* = 0.7 Hz, SC=C<u>H</u>), 4.21 (2H, q, *J* = 7.1 Hz, OCH_2), 3.82 (3H, s, OCH_3), 1.30 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0 (C), 160.88 (C), 150.0 (C), 146.7 (C), 143.2 (C), 138.8 (CH), 130.8 (CH), 129.4 (CH), 128.5 (C), 124.4 (CH), 121.2 (CH), 120.3 (CH), 114.3 (CH), 60.5 (CH_2), 55.4 (CH_3), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 386.1052, $C_{20}H_{20}NO_5S$ requires 386.1057.

E, *E* stereochemistry confirmed by NOESY δ 7.52 and 5.92:



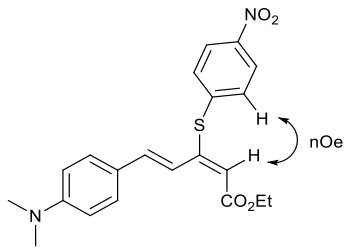
(2*E*, 4*E*)- Ethyl 5-(4-(dimethylamino)phenyl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100f)



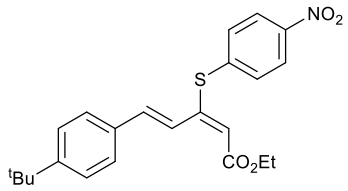
General procedure D was followed to yield product **100f** as red solid (25.8 mg, 0.06 mmol, 90%). Purified by column chromatography (eluent: hexane/ethyl acetate 7:1).

R_f 0.44 (5:1 hexane/ethyl acetate); Mp 146-149 °C ($CDCl_3$); ν_{max}/cm^{-1} 2980 (C-H), 1698 (C=O), 1595 (C=C, diene conj), 1520 (NO_2), 1554, 1476, 1444 (Ar C-C), 1338 (NO_2), 1164 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, dd, *J* = 15.6, 0.7 Hz, CH=C<u>H</u>CS), 8.14 (2H, d, *J* = 9.0 Hz, Ar-H), 7.49 (2H, d, *J* = 9.0 Hz, Ar-H), 7.41 (2H, d, *J* = 8.8 Hz, Ar-H), 7.29 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CHCS), 6.64 (2H, d, *J* = 8.8 Hz, Ar-H), 5.90 (1H, app. s, SC=C<u>H</u>), 4.22 (2H, q, *J* = 7.1 Hz, OCH_2), 3.00 (6H, s, NMe_2), 1.30 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.3 (C), 151.4 (C), 150.1 (C), 146.4 (C), 144.2 (C), 140.1 (CH), 130.2 (CH), 129.6 (CH), 124.3 (CH), 123.6 (CH), 119.1 (C), 118.7 (CH), 111.9 (CH), 60.3 (CH_2), 40.2 (CH_3), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 399.1374, $C_{21}H_{23}N_2O_4S$ requires 399.1373.

E, *E* stereochemistry confirmed by NOESY δ 7.49 and 5.90:



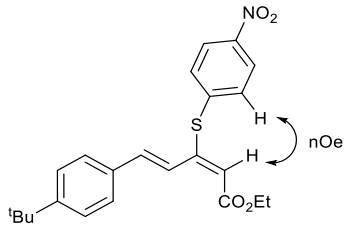
(2*E*, 4*E*)-Ethyl 5-(4-*tert*-butylphenyl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100g)



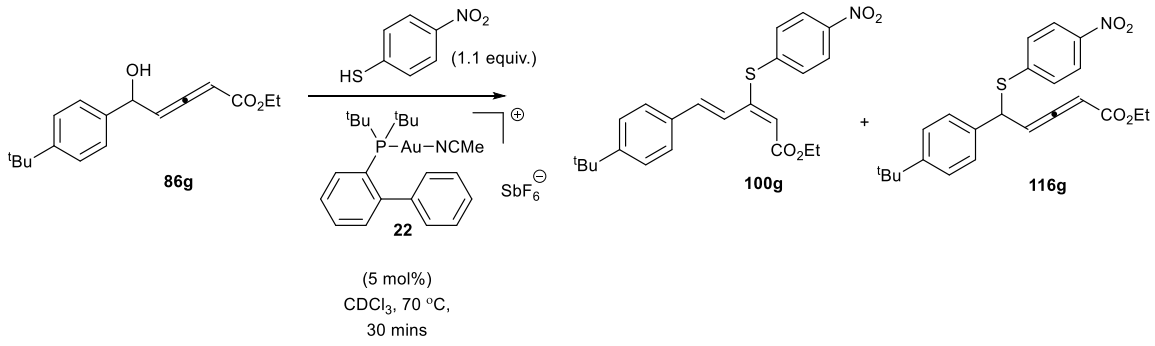
General procedure D was followed to yield product **100g** as a yellow solid (18.8 mg, 0.05 mmol, 68%). Purified by column chromatography (eluent: hexane/ethyl acetate 25:1 to 10:1).

R_f 0.70 (5:1 hexane/ethyl acetate); Mp 112-114 ^oC ($CDCl_3$); ν_{max}/cm^{-1} 2962 (C-H), 1703 (C=O), 1598 (C=C, diene conj), 1517 (NO_2), 1565, 1476, 1410 (Ar C-C), 1338 (NO_2), 1176 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (1H, dd, *J* = 15.8, 0.8 Hz, CH=C<u>H</u>CS), 8.17 (2H, d, *J* = 9.0 Hz, Ar-H), 7.52 (2H, d, *J* = 9.0 Hz, Ar-H), 7.44 (2H, d, *J* = 8.4 Hz, Ar-H), 7.36 (2H, d, *J* = 8.4 Hz, Ar-H), 7.31 (1H, d, *J* = 15.8 Hz, C<u>H</u>=CHCS), 5.97 (1H, app. s, SC=C<u>H</u>), 4.22 (2H, q, *J* = 7.1 Hz, OCH_2), 1.26-1.35 (12H, m, CH_3 + ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.9 (C), 153.1 (C), 149.8 (C), 146.7 (C), 143.1 (C), 139.1 (CH), 133.0 (C), 130.8 (CH), 127.7 (CH), 125.8 (CH), 124.4 (CH), 122.5 (CH), 121.0 (CH), 60.6 (CH_2), 34.8 (C), 31.2 (CH_3), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 412.1573, $C_{23}H_{26}NO_4S$ requires 412.1577.

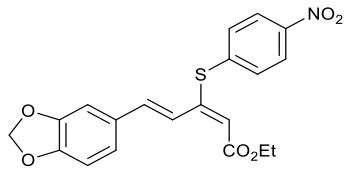
E, *E* stereochemistry confirmed by NOESY δ 7.52 and 7.31:



Au(I)-catalysis method: General procedure C was followed to yield product **100g** (7.7 mg, 0.02 mmol, 28%) in a 5:2 ratio (determined by ^1H NMR analysis of the crude product. Note: **116g** decomposed upon column chromatography). Purified by column chromatography (hexane/ethyl acetate 80:1 to 70:1 to 50:1 to 25:1). Characterisation as above.



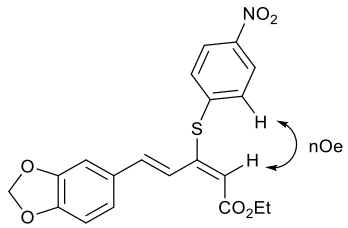
(2*E*, 4*E*)-Ethyl 5-(benzo[*d*][1,3]dioxo-5-yl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100h)



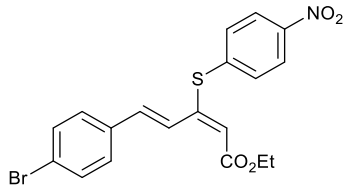
General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 20 min to yield product **100h** as a yellow solid (11.6 mg, 0.03 mmol, 47%). Purified by column chromatography (eluent: hexane/ethyl acetate 7:1).

R_f 0.44 (5:1 hexane/ethyl acetate); Mp 122-125 °C ($CDCl_3$); ν_{max}/cm^{-1} 2980 (C-H), 1699 (C=O), 1596 (C=C, diene conj), 1517 (NO_2), 1559, 1502, 1487, 1446 (Ar C-C), 1338 (NO_2), 1177 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13-8.26 (3H, m, Ar-H + CH=C<u>H</u>CS), 7.52 (2H, d, *J* = 8.9 Hz, Ar-H), 7.24 (1H, d, *J* = 15.8 Hz, C<u>H</u>=CHCS), 7.07 (1H, d, *J* = 1.5 Hz, Ar-H), 6.94 (1H, dd, *J* = 8.1, 1.6 Hz, Ar-H), 6.76 (1H, d, *J* = 8.0 Hz, Ar-H), 5.98 (2H, s, OCH_2O), 5.92 (1H, app. s, SC=C<u>H</u>), 4.21 (2H, q, *J* = 7.1 Hz, OCH_2), 1.30 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.0 (C), 149.8 (C), 149.1 (C), 148.4 (C), 146.8 (C), 143.1 (C), 138.8 (CH), 130.8 (CH), 130.2 (C), 124.4 (CH), 123.8 (CH), 121.6 (CH), 120.5 (CH), 108.5 (CH), 106.5 (CH), 101.5 (CH_2), 60.5 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 400.0854, $C_{20}H_{18}NO_6S$ requires 400.0849.

E, *E* stereochemistry confirmed by NOESY δ 7.52 and 5.29:



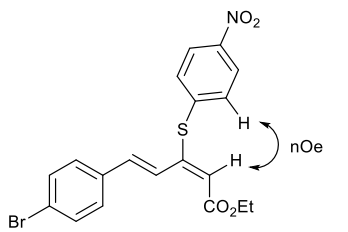
(2*E*, 4*E*)-Ethyl 5-(4-bromophenyl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100i)



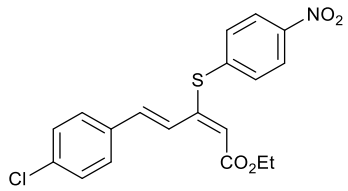
General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 20 min to yield product **100i** as a yellow solid (28.1 mg, 0.06 mmol, 93%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1).

R_f 0.71 (5:1 hexane/ethyl acetate); Mp:117-120 °C; ν_{max}/cm^{-1} 3065, 2980 (C-H), 1701 (C=O), 1614 (C=C, diene conj), 1596 (C=C, diene conj), 1515 (NO_2), 1566, 1556, 1485 (Ar C-C), 1336 (NO_2), 1174 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.36 (1H, dd, *J* = 15.9, 0.8 Hz, CH=C<u>H</u>CS), 8.18 (2H, d, *J* = 9.0 Hz, Ar-H), 7.53 (2H, d, *J* = 9.0 Hz, Ar-H), 7.47 (2H, d, *J* = 8.5 Hz, Ar-H), 7.36 (2H, d, *J* = 8.5 Hz, Ar-H), 7.25 (1H, d, *J* = 15.9 Hz, C<u>H</u>=CHCS), 5.94 (1H, app. s, SC=C<u>H</u>), 4.20 (2H, q, *J* = 7.1 Hz, OCH_2), 1.30 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.8 (C), 149.7 (C), 147.0 (C), 142.4 (C), 137.4 (CH), 134.6 (C), 132.0 (CH), 131.3 (CH), 129.2 (CH), 124.5 (CH), 123.9 (CH), 123.6 (C), 121.3 (CH), 60.7 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 434.0057, $C_{19}H_{17}NO_4SBr$ requires 434.0056.

E, *E* stereochemistry confirmed by NOESY δ 7.53 and 5.94:



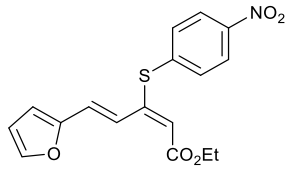
(2*E*, 4*E*)-Ethyl 5-(4-chlorophenyl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100j)



General procedure D was followed with the exception of the microwave conditions – reaction placed in microwave at 90 °C for 30 mins to yield product **100j** as a yellow solid (14.3 mg, 0.04 mmol, 49%). Purified by column chromatography (eluent: hexane/ethyl acetate 7:1).

R_f 0.64 (5:1 Hexane/ethyl acetate); Mp: 107-110 °C ($CDCl_3$); ν_{max}/cm^{-1} 2981 (C-H), 1703 (C=O), 1616 (C=C, diene conj), 1596 (C=C, diene conj), 1517 (NO_2), 1569, 1489, 1476 (Ar C-C), 1339 (NO_2), 1187 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, dd, *J* = 15.9, 0.9 Hz, CH=C<u>H</u>CS), 8.11 (2H, d, *J* = 9.0 Hz, Ar-H), 7.46 (2H, d, *J* = 9.0 Hz, Ar-H), 7.37 (2H, d, *J* = 8.4 Hz, Ar-H), 7.17-7.28 (3H, m, Ar-H + C<u>H</u>=CHCS), 5.87 (1H, app. s, SC=C<u>H</u>), 4.14 (2H, q, *J* = 7.1 Hz, OCH_2), 1.23 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.8 (C), 149.7 (C), 147.0 (C), 142.1 (C), 137.3 (CH), 135.3 (C), 134.2 (C), 131.2 (CH), 129.2 (CH), 129.1 (CH), 124.5 (CH), 123.8 (CH), 121.2 (CH), 60.7 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 390.0561, $C_{19}H_{17}ClNO_4S$ requires 390.0561.

(2*E*, 4*E*)-Ethyl 5-(furan-2-yl)-3-(4-nitrophenylthio)penta-2,4-dienoate (100l)

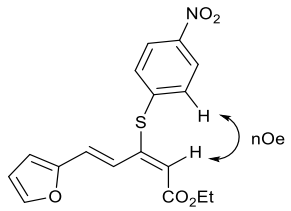


General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 20 mins to yield product **100l** as a pale yellow oil (19.0 mg, 0.06 mmol, 79%). Purified by column chromatography (eluent: hexane/ethyl acetate 7:1).

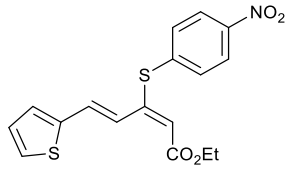
R_f 0.60 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3097, 2981 (C-H), 1702 (C=O), 1614 (C=C, diene conj), 1596 (C=C, diene conj), 1514 (NO_2), 1573, 1541, 1475 (Ar C-C), 1336 (NO_2), 1174 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.21 (1H, d, *J* = 16.1 Hz, CH=C<u>H</u>CS), 8.16 (2H, d, *J* = 9.0 Hz, Ar-H), 7.49 (2H, d, *J* = 9.0 Hz, Ar-H), 7.45 (1H, d,

J = 1.7 Hz, furan-H), 7.11 (1H, d, *J* = 16.1 Hz, C<u>H</u>=CHCS), 6.48 (1H, d, *J* = 3.4 Hz, furan-H), 6.42 (1H, dd, *J* = 3.4, 1.7 Hz, furan-H), 6.00 (1H, s, SC=C<u>H</u>), 4.23 (2H, q, *J* = 7.1 Hz, OCH_2), 1.30 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.8 (C), 152.0 (C), 148.5 (C), 146.6 (C), 144.4 (CH), 143.3 (C), 130.2 (CH), 125.9 (CH), 124.4 (CH), 122.1 (CH), 121.6 (CH), 113.3 (CH), 112.3 (CH), 60.6 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 346.0747, $C_{17}H_{16}NO_5S$ requires 346.0744.

.*E, E* stereochemistry confirmed by NOESY δ 7.11 and 6.00:



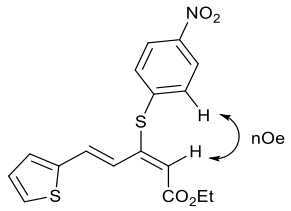
(2*E*, 4*E*)-Ethyl 3-(4-nitrophenylthio)-5-(thiophen-2-yl)penta-2,4-dienoate (100m)



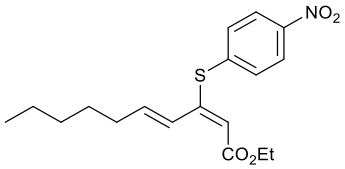
General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 20 mins to yield product **100m** as a yellow oil (21.6 mg, 0.06 mmol, 84%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1).

R_f 0.60 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3099, 2980 (C-H), 1698 (C=O), 1596 (C=C, diene conj), 1513 (NO_2), 1562, 1475, 1423 (Ar C-C), 1335 (NO_2), 1174 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (1H, d, *J* = 15.5 Hz, CH=C<u>H</u>CS), 8.16 (2H, d, *J* = 9.0 Hz, Ar-H), 7.50 (2H, d, *J* = 9.0 Hz, Ar-H), 7.46 (1H, d, *J* = 15.5 Hz, C<u>H</u>=CHCS), 7.32 (1H, dt, *J* = 5.0, 0.8 Hz, thiophene-H), 7.12 (1H, dt, *J* = 3.6, 0.8 Hz, thiophene-H), 7.00 (1H, dd, *J* = 5.0, 3.6 Hz, thiophene-H), 5.97 (1H, s, SC=C<u>H</u>), 4.22 (2H, q, *J* = 7.1 Hz, OCH_2), 1.31 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.8 (C), 148.7 (C), 146.7 (C), 143.1 (C), 141.3 (C), 131.9 (CH), 130.5 (CH), 129.6 (CH), 128.1 (CH), 127.8 (CH), 124.4 (CH), 122.8 (CH), 121.6 (CH), 60.6 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 362.0515, $C_{17}H_{16}NO_4S_2$ requires 362.0515.

E, *E* stereochemistry confirmed by NOESY δ 7.50 and 5.97:



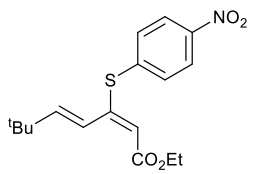
(2*E*, 4*E*)-Ethyl 3-(4-nitrophenylthio)deca-2,4-dienoate (100a)



General procedure D was followed with the exception of microwave conditions - reaction placed in microwave at 90 °C for 60 mins to yield product **100a** as a yellow oil (6.9 mg, 0.02 mmol, 42%). Purified by column chromatography (eluent: hexane/ethyl acetate, 80:1 to 50:1).

R_f 0.53 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2929 (C-H), 1736 (C=O), 1597 (C=C, diene), 1576 (Ar C-C), 1518 (NO_2), 1340 (NO_2), 1185 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (2H, d, *J* = 8.9 Hz, Ar-H), 7.45-7.54 (3H, m, Ar-H + CH_2CH=C<u>H</u>CS), 6.54 (1H, dt, *J* = 14.3, 7.0 Hz, CH_2C<u>H</u>=CHCS), 5.79 (1H, s, SC=C<u>H</u>), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2), 2.20 (2H, dq, *J* = 7.2, 1.1 Hz, C<u>H</u>$_2$CH=CH), 1.15-1.44 (9H, m, alkyl H's), 0.85 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ 164.7 (C), 150.4 (C), 146.9 (C), 143.4 (CH), 142.8 (C), 131.4 (CH), 124.3 (CH), 124.2 (CH), 118.9 (CH), 60.4 (CH_2), 33.0 (CH_2), 31.3 (CH_2), 28.3 (CH_2), 22.4 (CH_2), 14.3 (CH_3), 13.9 (CH_3); Found (FTMS + p APCI) $[M + H]^+$ 350.1424, $C_{18}H_{24}NO_4S$ requires 350.1421.

(2*E*, 4*E*)-Ethyl 6,6-dimethyl-3-(4-nitrophenylthio)hepta-2,4-dienoate (100n)

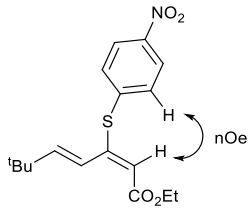


General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 70 °C for 60 mins to yield product **100n** as a pale yellow oil (19.2

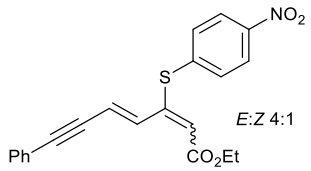
mg, 0.05 mmol, 80%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1).

R_f 0.78 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2960, 2886 (C-H), 1705 (C=O), 1628 (C=C, diene conj), 1597 (C=C, diene conj), 1518 (NO_2), 1567, 1476 (Ar C-C), 1337 (NO_2), 1175 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (2H, d, *J* = 8.9 Hz, Ar-H), 8.42-8.52 (3H, m, Ar-H + CH=C<u>H</u>CS), 6.52 (1H, d, *J* = 15.8 Hz, C<u>H</u>=CHCS), 5.78 (1H, s, SC=C<u>H</u>), 4.17 (2H, q, *J* = 7.1 Hz, OCH_2), 1.27 (3H, t, *J* = 7.1 Hz, CH_3), 1.03 (9H, s, ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.8 (C), 153.1 (CH), 151.2 (C), 146.9 (C), 142.6 (C), 131.7 (CH), 124.2 (CH), 120.3 (CH), 118.8 (CH), 60.4 (CH_2), 34.1 (C), 29.0 (CH_3), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 336.1262, $C_{17}H_{22}NO_4S$ requires 336.1264.

.*E*, *E* stereochemistry confirmed by NOESY δ 8.42 and 5.78:



(2*E*, 4*E*)-Ethyl 3-(4-nitrophenylthio)-7-phenylhepta-2,4-dien-6-ynoate (100o)

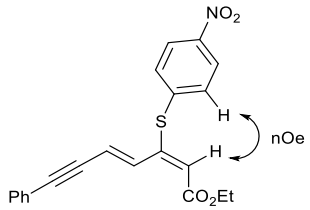


General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 20 mins to yield product **100o** as a yellow oil (22.9 mg, 0.06 mmol, 85%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1).

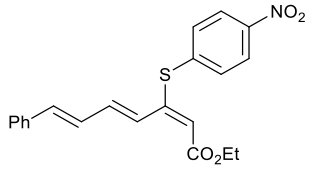
R_f 0.65 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3063 (C-H), 2981 (C-H), 2981 (C≡C), 1706 (C=O), 1598 (C=C, diene conj), 1517 (NO_2), 1577, 1561, 1476, 1442 (Ar C-C), 1338 (NO_2), 1186 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (2H, d, *J* = 9.0 Hz, Ar-H, major), 8.16 (2H', d, *J* = 9.0 Hz, Ar-H, minor), 8.13 (1H + 1H', dd, *J* = 15.7, 0.9 Hz, C≡CCH=C<u>H</u>), 7.54 (2H', d, *J* = 9.0 Hz, Ar-H, minor), 7.48 (2H, d, *J* = 9.0 Hz, Ar-H, major), 7.42-7.45 (2H + 2H', m, Ar-H), 7.31-7.36 (3H + 3H', m, Ar-H), 6.64 (1H + 1H', dd, *J* = 15.7 Hz, 0.6 Hz, C≡CC<u>H</u>=CH), 6.00 (1H, app. t, *J* = 0.8 Hz, major, SC=C<u>H</u>), 5.92

(1H, app. t, J = 1.0 Hz, minor, SC=C<u>H</u>), 4.23 (2H, q, J = 7.1 Hz, OCH_2, major), 4.16 (2H', q, J = 7.1 Hz, OCH_2, minor), 1.30 (3H, t, J = 7.1 Hz, CH_3, major), 1.25 (3H', t, J = 7.1 Hz, CH_3, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.3 (C, major + minor), 149.3 (C, minor), 147.6 (C, major), 147.2 (C, minor), 146.8 (C, major), 142.5 (C, major), 141.7 (C, minor), 134.9 (CH, major), 133.1 (CH, minor), 132.4 (CH, minor), 131.9 (CH, major), 131.4 (CH, minor), 130.5 (CH, major), 129.0 (CH, major + minor), 128.5 (CH, minor), 128.4 (CH, major), 124.5 (CH, major), 124.2 (CH, minor), 123.0 (CH, major), 124.1 (C, minor), 122.6 (C, major), 121.3 (CH, minor), 119.4 (CH, major), 115.7 (CH, minor), 100.9 (C, minor), 97.8 (C, major), 88.2 (C, major), 87.0 (C, minor), 60.8 (CH_2, major), 60.7 (CH_2, minor), 14.22 (CH_3, major), 14.17 (CH_3, minor); Found (FTMS+ p APCI) $[M + H]^+$ 380.0951, $C_{21}H_{18}NO_4S$ requires 380.0951.

E, *E* stereochemistry for major isomer confirmed by NOESY δ 7.48 and 6.00:



(2*E*, 4*E*, 6*E*)-Ethyl 3-(4-nitrophenylthio)-7-phenylhepta-2,4,6-trienoate (100p)

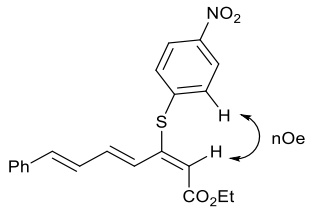


General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 20 mins to yield product **100p** as a yellow solid (10.2 mg, 0.03 mmol, 38%). Purified by column chromatography (eluent: hexane/ethyl acetate 25:1 to 10:1).

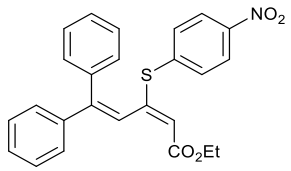
R_f 0.66 (5:1 hexane/ethyl acetate); Mp 91-94 °C ($CDCl_3$); ν_{max}/cm^{-1} 2981 (C-H), 1702 (C=O), 1592 (C=C, triene conj), 1515 (NO_2), 1575, 1552, 1476 (Ar C-C), 1338 (NO_2), 1176 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (2H, d, J = 9.0 Hz, Ar-H), 7.89 (1H, d, J = 14.9 Hz, PhC<u>H</u>=CH), 7.50 (2H, d, J = 9.0 Hz, Ar-H), 7.24-7.44 (5H, m, Ar-H), 7.45 (1H, dd, J = 14.9, 10.7 Hz, PhCH=C<u>H</u>), 6.98 (1H, dd, J = 16.4, 10.7 Hz, PhCH=CHCH=C<u>H</u>), 6.73 (1H, d, J = 16.4 Hz, PhCH=CHC<u>H</u>=CH), 5.92 (1H, s, SC=C<u>H</u>), 4.20 (2H, q, J = 7.1 Hz, OCH_2), 1.30 (3H, t, J = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz,

$CDCl_3$) δ 164.8 (C), 149.3 (C), 146.8 (C), 143.1 (C), 139.6 (CH), 138.4 (CH), 136.4 (C), 130.7 (CH), 128.8 (CH), 128.7 (CH), 128.0 (CH), 127.1 (CH), 127.0 (CH), 124.4 (CH), 120.9 (CH), 60.6 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 382.1108, $C_{21}H_{20}NO_4S$ requires 382.1108.

E, *E*, *E* stereochemistry confirmed by NOESY δ 7.50 and 5.92:



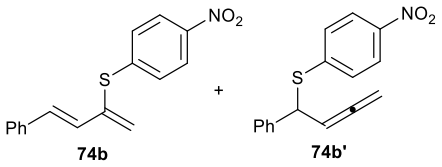
Ethyl (*E*)-3-((4-Nitrophenyl)thio)-5,5-diphenylpenta-2,4-dienoate (100q)



General procedure D was followed to yield product **100q** as a yellow oil (29.3 mg, 0.07 mmol, 100%). Purified by column chromatography (eluent: hexane/ethyl acetate 20:1 to 10:1).

R_f 0.30 (10:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3056, 2980 (C-H), 1703 (C=O), 1596 (C=C, diene conj), 1516 (NO_2), 1493, 1476, 1443 (Ar C-C), 1339 (NO_2), 1183 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.13 (2H, d, *J* = 8.9 Hz, Ar-H), 7.27-7.41 (8H, m, Ar-H), 7.20-7.23 (2H, m, Ar-H), 7.19 (1H, d, *J* = 1.7 Hz, C=C<u>H</u>CS), 7.13-7.17 (2H, m, Ar-H), 5.68 (1H, d, *J* = 1.7 Hz, SC=C<u>H</u>), 4.14 (2H, q, *J* = 7.1 Hz, OCH_2), 1.23 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 164.6 (C), 153.7 (C), 148.5 (C), 147.4 (C), 141.5 (C), 141.0 (C), 139.2 (C), 133.5 (CH), 130.4 (CH), 128.55 (CH), 128.51 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 124.1 (CH), 123.2 (CH), 118.4 (CH), 60.3 (CH_2), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 432.1262, $C_{25}H_{22}NO_4S$ requires 432.1264.

(*E*)-(4-Nitrophenyl)(4-phenylbuta-1,3-dien2-yl)sulfane (x)

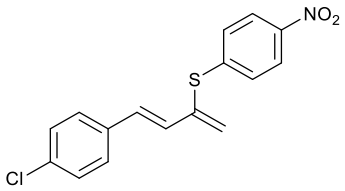


5:1 **74b**:**74b'**

General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 60 mins to yield product **74b** as the major product and the formal S_N2 product (**74b'**) as a side product in a 5:1 ratio (14.3 mg, 0.05 mmol, 72%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1). **74b** and **74b'** were inseparable by chromatography, only the major **74b** is characterised below.

R_f 0.71 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3026 (C-H), 1594 (C=C, diene conj), 1509 (NO_2), 1576, 1476, 1448 (Ar C-C), 1335 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 9.1 Hz, Ar-H), 7.25-7.43 (7H, m, Ar-H), 6.96 (1H, d, *J* = 15.6 Hz, CH=C<u>H</u>CS), 6.89 (1H, d, *J* = 15.6 Hz, C<u>H</u>=CHCS), 6.00 (1H, s, C=C<u>H$_2$</u>), 5.85 (1H, s, C=C<u>H$_2$</u>); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 146.2 (C), 137.5 (C), 135.9 (C), 134.2 (CH), 128.7 (CH), 128.8 (CH), 127.9 (CH_2), 127.8 (C), 127.1 (CH), 126.9 (CH), 126.6 (CH), 124.0 (CH); Found (FTMS+ p APCI) $[M + H]^+$ 284.0737, $C_{16}H_{14}NO_2S$ requires 284.0740.

(*E*)-(4-(4-Chlorophenyl)buta-1,3-dien-2-yl)(4-nitrophenyl)sulfane (74j)

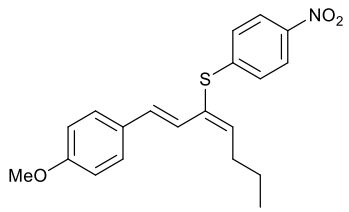


General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 60 mins to yield product **74j** (20.3 mg, 0.06 mmol, 91%). Purified by column chromatography (eluent: hexane/ethyl acetate 10:1). Note that the product is very unstable and decomposes at room temperature in <1 h.

R_f 0.59 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3096, 2921 (C-H), 1594 (C=C, diene conj), 1511 (NO_2), 1576, 1489, 1476, 1404 (Ar C-C), 1336 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (2H, d, *J* = 9.1 Hz, Ar-H), 7.37 (2H, d, *J* = 9.1 Hz, Ar-H), 7.28 (4H, m, Ar-H), 6.91 (1H, d, *J* = 16.0 Hz, CH=C<u>H</u>CS), 6.85 (1H, d, *J* = 16.0 Hz, C<u>H</u>=CHCS), 6.01 (1H, s, C=CH_2), 5.86 (1H, s, C=CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.9 (C), 137.4 (C), 134.5

(C), 134.2 (C), 132.5 (CH), 129.1 (C), 129.0 (CH), 128.9 (CH), 128.2 (CH_2), 128.1 (CH), 127.2 (CH), 124.0 (CH); Found (FTMS+ p APCI) $[M + H]^+$ 318.0344, $C_{16}H_{13}NO_2SCl$ requires 318.0350.

((1*E*, 3*E*)-1-(4-Methoxyphenyl)hepta-1,3-dien-3-yl)(4-nitrophenyl)sulfane (74e)



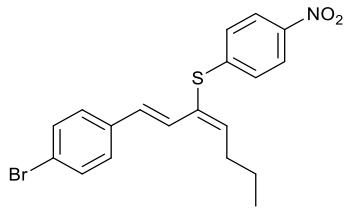
In a sealed tube was placed $InCl_3$ (1.0 mg, 5 mol%) and 4-nitrothiophenol (10.9 mg, 0.07 mmol, 1.0 equiv.), which were then dissolved in $CDCl_3$ (0.35 ml). A solution of allenol **73e** (22.8 mg, 0.105 mmol, 1.5 equiv.) in $CDCl_3$ (0.15 ml) was added to the sealed tube and washed in with $CDCl_3$ (0.20 ml). The sealed tube was then placed in a silicon oil bath at 90 ^oC and left stirring for 16 h (CEM Discover microwave does not heat continuously beyond 60 min, so for extended reaction times, conventional heating was used) to yield product **74e** as a yellow oil (21.8 mg, 0.06 mmol, 88%) with a 2:1 mixture of *E*/*Z* isomers. Purified by column chromatography (hexane/ethyl acetate 20:1).

Note: Under standard microwave conditions (90 ^oC, 60 min), the yield was 69%

R_f 0.51 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2958, 2930, 2870, 2835 (C-H), 1604 (C=C, diene conj), 1576 (C=C, diene conj), 1508 (NO_2), 1476, 1462, 1420 (Ar C-C), 1333 (NO_2), 1246 (C-O-C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (2H', d, *J* = 8.9 Hz, minor, Ar-H), 8.06 (2H, d, *J* = 9.1 Hz, major, Ar-H), 7.27-7.36 (4H + 4H', m, Ar-H), 7.04 (1H, dd, *J* = 15.5, 0.8 Hz, CH=C<u>H</u>CS), 6.89 (1H, d, *J* = 15.5 Hz, C<u>H</u>=CHCS), 6.80-6.85 (2H + 2H', m, Ar-H), 6.50 (1H', t, *J* = 7.5 Hz, C=C<u>H</u>CH_2), 6.36 (1H, t, *J* = 7.7 Hz, C=C<u>H</u>CH_2), 3.80 (3H, s, OCH_3), 3.79 (3H', s, OCH_3), 2.40-5.51 (2H + 2H', m, C=CHC<u>H_2</u>), 1.58 (2H, sext, *J* = 7.4 Hz, CH_2C<u>H_2</u>CH_3), 1.47 (2H', sext, *J* = 7.4 Hz, CH_2C<u>H_2</u>CH_3), 1.07 (3H, t, *J* = 7.4 Hz, CH_3), 0.93 (3H', t, *J* = 7.4 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 159.8 (C, major), 159.5 (C, minor), 148.4 (C, major), 147.2 (C, minor), 145.5 (CH, major), 145.3 (CH, minor), 145.0 (C, major + minor), 133.2 (CH, major), 130.6 (CH, minor), 129.44 (C, major + minor), 129.37 (C, minor), 129.3 (C, major), 128.2 (CH, minor), 127.9 (CH, major), 125.9 (CH, minor), 125.8 (CH, major), 124.4 (CH, minor), 124.2 (CH, major), 119.9 (CH, major + minor), 114.2 (CH, major), 114.1 (CH, minor), 55.33 (CH_3,

major), 55.31 (CH_3, minor), 32.7 (CH_2, minor), 31.6 (CH_2, major), 22.5 (CH_2, major), 22.4 (CH_2, minor), 13.89 (CH_3, major), 13.87 (CH_3, minor); Found (FTMS+ p APCI) $[M + H]^+$ 356.1316, $C_{20}H_{22}NO_3S$ requires 356.1315.

((1*E*,3*E*)-1-(4-Bromophenyl)hepta-1,3-dien-3-yl)(4-nitrophenyl)sulfane (74i)

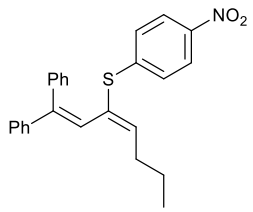


In a sealed tube was placed $InCl_3$ (1.0 mg, 5 mol%) and 4-nitrothiophenol (10.9 mg, 0.07 mmol, 1.0 equiv.), which were then dissolved in $CDCl_3$ (0.35 ml). A solution of allenol **73i** (22.8 mg, 0.105 mmol, 1.5 equiv.) in $CDCl_3$ (0.15 ml) was added to the sealed tube and washed in with $CDCl_3$ (0.20 ml). The sealed tube was then placed in a silicon oil bath at 90 °C and left stirring for 16 h (CEM Discover microwave does not heat continuously beyond 60 min, so for extended reaction times, conventional heating was used) to yield product **74i** as a yellow oil (21.9 mg, 0.05 mmol, 77%) with a 2:1 mixture of *E*/*Z* isomers. Purified by column chromatography (hexane/ethyl acetate 50:1 to 25:1).

R_f 0.62 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2958, 2928, 2873 (C-H), 1576 (C=C, diene conj), 1509 (NO_2), 1485, 1399 (Ar C-C), 1335 (NO_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (2H', d, *J* = 9.1 Hz, Ar-H, minor), 8.06 (2H, d, *J* = 9.1 Hz, Ar-H, major), 7.42 (2H, d, *J* = 8.4 Hz, Ar-H), 7.40 (2H', d, *J* = 8.4 Hz, Ar-H), 7.28 (2H, d, *J* = 9.1 Hz, Ar-H), 7.27 (2H', *J* = 9.1 Hz, Ar-H), 7.23 (2H, d, *J* = 8.4 Hz, Ar-H), 7.21 (2H', d, *J* = 8.4 Hz, Ar-H), 7.16 (1H, dd, *J* = 15.5, 0.9 Hz, CH=C<u>H</u>CS), 6.91 (1H', d, *J* = 15.5 Hz, CH=C<u>H</u>CS), 6.88 (1H, d, *J* = 15.5 Hz, C<u>H</u>=CHCS), 6.78 (1H', d, *J* = 15.5 Hz, C<u>H</u>=CHCS), 6.58 (1H', t, *J* = 7.5 Hz, SC=C<u>H</u>CH_2), 6.45 (1H, t, *J* = 7.7 Hz, SC=C<u>H</u>CH_2), 2.41-2.51 (2H + 2H', m, =CHC<u>H_2</u>), 1.54-1.64 (2H, m, CH_2C<u>H_2</u>CH_3), 1.48 (2H', sext, *J* = 7.4 Hz, CH_2C<u>H_2</u>CH_3), 1.03 (3H, t, *J* = 7.3 Hz, CH_3), 0.93 (3H', t, *J* = 7.4 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.9 (C, major), 147.5 (CH, major), 147.4 (CH, minor), 146.7 (C, minor), 145.1 (C, major + minor), 137.8 (CH, minor), 135.55 (C, minor), 135.51 (C, major) 132.4 (CH, major), 131.81 (CH, major), 131.76 (CH, minor), 129.8 (CH, minor), 129.4 (CH, major), 128.5 (C, minor), 128.3 (CH, major), 128.1 (CH, minor), 127.6 (C, major), 125.88 (CH, minor), 125.85 (CH, major), 124.1 (CH, minor), 124.0 (CH, major), 122.1 (C,

major), 121.7 (C, minor), 32.8 (CH_2, minor), 31.5 (CH_2, major), 22.4 (CH_2, major), 22.3 (CH_2, minor), 13.9 (2 x CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 404.0308, $C_{19}H_{19}NO_2SBr$ requires 404.0314.

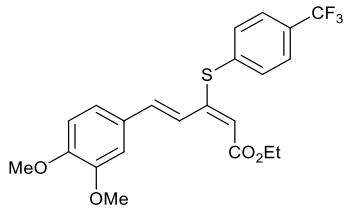
(*E*)-(1,1-Diphenylhepta-1,3-dien-3-yl)(4-nitrophenyl)sulfane (74q)



General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 °C for 60 mins to yield product **74q** as a yellow oil with 1:1 *E*/*Z* (14.9 mg, 0.04 mmol, 59%). Purified by column chromatography (eluent: hexane/ethyl acetate 80:1 to 70:1 to 25:1).

R_f 0.51 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3056, 2958, 2928, 2870 (C-H), 1593 (C=C, diene conj), 1508 (NO_2), 1575, 1476, 1443 (Ar C-C), 1333 (NO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04-8.11 (2H + 2H', m, Ar-H), 7.13-7.36 (10H + 10H', m, Ar-H), 7.03-7.11 (1H + 1H', m, Ar-H), 7.02-7.05 (1H + 1H', m, Ar-H), 6.60 (1H', app. q, *J* = 1.3 Hz, C=C<u>H</u>CS), 6.53 (1H, app. q, *J* = 1.1 Hz, C=C<u>H</u>CS), 6.16 (1H, td, *J* = 7.4, 1.1 Hz, C=C<u>H</u>CH_2), 6.11 (1H', td, *J* = 7.5, 1.4 Hz, C=C<u>H</u>CH_2), 2.24-2.18 (2H, m, CHC<u>H_2</u>), 2.20-2.14 (2H', m, CHC<u>H_2</u>), 1.40 (2H', sext, *J* = 7.5 Hz, CH_2C<u>H_2</u>CH_3), 1.26 (2H, sext, *J* = 7.4 Hz, CH_2C<u>H_2</u>CH_3), 0.94 (3H, t, 7.4 Hz, CH_3), 0.78 (3H', t, *J* = 7.5 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 147.6 (C), 146.8 (C), 146.3 (C), 145.3 (C), 145.2 (C), 143.7 (C), 142.4 (C), 142.3 (C), 139.78 (C), 139.77 (C), 130.0 (CH), 129.97 (CH), 128.4 (CH), 128.19 (2 x CH), 128.16 (CH), 128.08 (CH), 128.05 (CH), 127.92 (CH), 127.88 (CH), 127.78 (CH), 127.56 (CH), 127.52 (CH), 127.5 (CH), 127.30 (2 x C), 127.28 (CH), 127.1 (CH), 124.3 (CH), 123.77 (CH), 123.67 (CH), 122.9 (CH), 32.7 (CH_2), 32.5 (CH_2), 22.0 (CH_2), 21.97 (CH_2), 13.93 (CH_3), 13.70 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 402.1518, $C_{25}H_{24}NO_2S$ requires 402.1522.

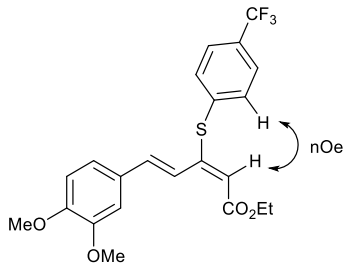
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(4-(trifluoromethylphenylthio)penta-2,4-dienoate (100cc)



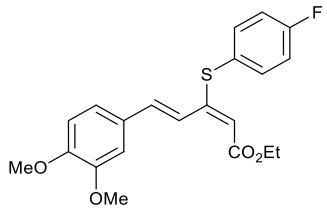
General procedure D was followed to yield product **100cc** as a yellow solid (23.9 mg, 0.05 mmol, 74%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.36 (5:1 hexane/ethyl acetate); Mp 77-78 ^oC ($CDCl_3$); ν_{max}/cm^{-1} 2936 (C-H), 1699 (C=O), 1599 (C=C, diene conj), 1580 (C=C, diene conj), 1557, 1511, 1464 (Ar C-C), 1321 (C-F), 1160 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (1H, dd, *J* = 14.9, 0.4 Hz, CH=C<u>H</u>CS), 7.56-7.64 (4H, m, Ar-H), 7.33 (1H, d, *J* = 14.9 Hz, C<u>H</u>=CHCS), 7.06-7.12 (2H, m, Ar-H), 6.84 (1H, d, *J* = 8.2 Hz, Ar-H), 5.60 (1H, app. s, SC=C<u>H</u>), 4.16 (2H, q, *J* = 7.1 Hz, OCH_2), 3.93 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 1.28 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.2 (C), 152.7 (C), 150.4 (C), 149.2 (C), 137.6 (CH), 135.0 (C), 133.1 (CH), 130.6 (C, q, *J* = 32.8 Hz), 129.0 (C), 125.6 (C, q, *J* = 272.1 Hz), 126.4 (CH, q, *J* = 3.7 Hz), 121.8 (CH), 121.7 (CH), 116.5 (CH), 111.1 (CH), 109.7 (CH), 60.2 (CH_2), 55.96 (CH_3), 55.93 (CH_3), 14.3 (CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 439.1177, $C_{22}H_{22}O_4SF_3$ requires 439.1185.

E, *E* stereochemistry confirmed by NOESY δ 7.56-7.64 and 5.60:



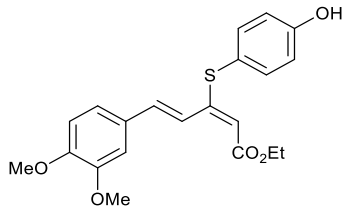
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(4-fluorophenylthio)penta-2,4-dienoate (100dc)



General procedure D was followed to yield product **100dc** as a yellow solid (17.6 mg, 0.05 mmol, 65%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.29 (5:1 hexane/ethyl acetate); Mp 113-115 ^oC ($CDCl_3$); ν_{max}/cm^{-1} 2935 (C-H), 1697 (C=O), 1598 (C=C, diene conj), 1555, 1511 (Ar C-C), 1489 (C-F), 1177 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 8.22 (1H, dd, *J* = 16.1, 0.8 Hz, CH=C<u>H</u>CS), 7.50-7.55 (2H, m, Ar-H), 7.34 (1H, d, *J* = 16.1 Hz, C<u>H</u>=CHCS), 7.08-7.17 (4H, m, Ar-H), 6.86 (1H, d, *J* = 8.3 Hz, Ar-H), 5.21 (1H, app. s, SC=C<u>H</u>), 4.12 (2H, q, *J* =7.1 Hz, OCH_2), 3.94 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 1.24 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.3 (C), 162.0 (C, d, *J* 251 Hz), 155.9 (C), 150.2 (C), 149.2 (C), 137.6 (CH, d, *J* = 8.5 Hz), 136.1 (CH), 129.2 (C), 125.3 (C, d, *J* = 3.5 Hz), 121.9 (CH), 121.3 (CH), 117.3 (CH, d, *J* = 22.0 Hz), 112.3 (CH), 111.1 (CH), 109.7 (CH), 59.9 (CH_2), 55.95 (CH_3), 55.94 (CH_3), 14.3 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 389.1209, $C_{21}H_{22}FO_4S$ requires 389.1217.

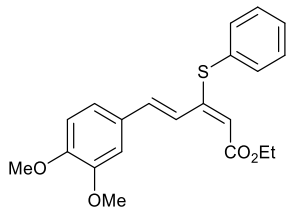
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(4-hydroxyphenylthio)penta-2,4-dienoate (100ec)



General procedure D was followed with the exception of microwave conditions – reaction placed in microwave at 90 ^oC for 60 mins to yield product **100ec** as a yellow oil (4.4 mg, 0.01 mmol, 29%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1 to 3:1); note that the product is unstable and begins to decompose on column.

R_f 0.14 (3:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 3412 (O-H), 2935 (C-H), 1665 (C=O), 1581 (C=C, diene conj), 1556, 1512 (Ar C-C), 1167 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$), δ 8.21 (1H, d, *J* = 16.1 Hz, CH=C<u>H</u>CS), 7.39-7.41 (3H, m, Ar-H + C<u>H</u>=CHCS), 7.06-7.16 (2H, m, Ar-H), 6.91 (2H, d, *J* = 8.6 Hz, Ar-H), 6.85 (1H, d, *J* = 8.2 Hz, Ar-H), 5.17 (1H, s, SC=C<u>H</u>), 4.12 (2H, q, *J* = 7.1 Hz, OCH_2), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 1.24 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 165.7 (C), 157.4 (C), 157.3 (C), 156.1 (C), 150.1 (C), 149.2 (C), 137.7 (CH), 135.6 (CH), 132.9 (CH), 129.3 (C), 121.6 (CH), 117.0 (CH), 116.1 (CH), 111.2 (CH), 109.7 (CH), 59.9 (CH_2), 55.97 (CH_3), 55.94 (CH_3), 14.4 (CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 387.1261, $C_{21}H_{23}O_5S$ requires 387.1261.

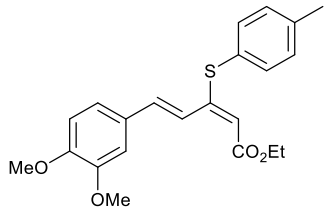
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(phenylthio)penta-2,4-dienoate (100ac)



Prepared by general procedure D to yield product **100ac** as a yellow solid (19 mg, 0.05 mmol, 73%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.25 (5:1 hexane/ethyl acetate); Mp 102-103 °C ($CDCl_3$); ν_{max}/cm^{-1} 3058 (C-H_{Ar}) 2934 (C-H alkyl), 1695 (C=O), 1615 (C=C, diene conj), 1597 (C=C, diene conj), 1580, 1556, 1511 (Ar C-C), 1175 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$), δ 8.25 (1H, dd, *J* = 16.0, 0.9 Hz, CH=C<u>H</u>CS), 7.49-7.56 (2H, m, Ar-H), 7.40-7.46 (3H, m, Ar-H), 7.34 (1H, d, *J* = 16.0 Hz, C<u>H</u>=CHCS), 7.10-7.16 (2H, m, Ar-H), 6.85 (1H, d, *J* = 1.7 Hz, Ar-H), 5.31 (1H, app. s, SC=C<u>H</u>), 4.11 (2H, q, *J* = 7.1 Hz, OCH_2), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 1.23 (3H, t, *J* = 7.1 Hz,CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.5 (C), 155.7 (C), 150.1 (C), 149.1 (C), 136.1 (CH), 135.1 (CH), 129.8 (CH), 129.7 (C), 129.4 (CH), 129.3 (C), 122.1 (CH), 121.6 (CH), 112.8 (CH), 111.1 (CH), 109.7 (CH), 59.9 (CH_2), 55.95 (CH_3), 55.94 (CH_3), 14.3 (CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 371.1310, $C_{21}H_{23}O_4S$ requires 371.1312.

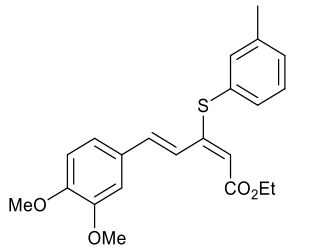
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(*p*-tolylthio)penta-2,4-dienoate (100gc)



General procedure D was followed to yield product **100gc** as a yellow solid (20.1 mg, 0.05 mmol, 72%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.31 (5:1 hexane/ethyl acetate); Mp 109-112 °C ($CDCl_3$); ν_{max}/cm^{-1} 2934 (C-H), 1697 (C=O), 1615 (C=C, diene conj), 1597 (C=C, diene conj), 1581, 1556, 1511 (Ar C-C), 1176 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.23 (1H, dd, *J* = 16.1, 0.7 Hz, CH=C<u>H</u>CS), 7.41 (3H, m, Ar-H), 7.23 (2H, m, Ar-H + C<u>H</u>=CHCS), 7.12 (2H, m, Ar-H), 6.85 (1H, d, *J* = 8.3 Hz, Ar-H), 5.25 (1H, app. s, SC=C<u>H</u>), 4.13 (2H, q, *J* = 7.1 Hz, OCH_2), 3.93 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.40 (3H, s, $ArCH_3$), 1.24 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.5 (C), 156.5 (C), 150.1 (C), 149.1 (C), 139.9 (C), 135.8 (CH), 135.4 (CH), 130.6 (CH), 129.3 (C), 126.3 (C), 122.2 (CH), 121.5 (CH), 111.9 (CH), 111.1 (CH), 109.7 (CH), 59.8 (CH_2), 55.95 (CH_3), 55.94 (CH_3), 21.4 (CH_3), 14.4 (CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 385.1470, $C_{22}H_{24}O_4S$ requires 385.1468.

(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(*m*-tolylthio)penta-2,4-dienoate (100hc)

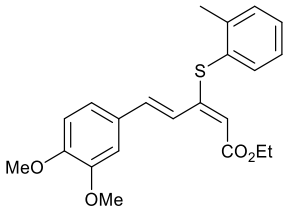


General procedure D was followed to yield product **100hc** as a yellow solid (14.7 mg, 0.04 mmol, 54%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.28 (5:1 hexane/ethyl acetate); Mp: 69-70 °C ($CDCl_3$); ν_{max}/cm^{-1} 2932 (C-H), 1697 (C=O), 1615 (C=C, diene conj), 1580, 1555, 1511 (Ar C-C), 1159 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.23 (1H, dd, *J* = 16.1, 0.8 Hz, CH=C<u>H</u>CS), 7.29-7.39 (4H, m, Ar-H + C<u>H</u>=CHCS), 7.19-7.25 (1H, m, Ar-H), 7.07-7.16 (2H, m, Ar-H), 6.85 (1H, d, *J* = 8.2

Hz, Ar-H), 5.31 (1H, app. s, SC=C<u>H</u>), 4.12 (2H, q, *J* = 7.1 Hz, OCH_2), 3.94 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.38 (3H, s, $ArCH_3$), 1.24 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.5 (C), 156.0 (C), 150.1 (C), 149.2 (C), 139.7 (C), 136.0 (CH), 135.7 (CH), 132.2 (CH), 130.3 (CH), 129.8 (C), 129.6 (CH), 129.3 (C), 122.2 (CH), 121.6 (CH), 112.6 (CH), 111.1 (CH), 109.7 (CH), 59.9 (CH_2), 55.9 (2 x CH_3), 21.3 (CH_3), 14.4 (CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 385.1470, $C_{22}H_{24}O_4S$ requires 385.1468.

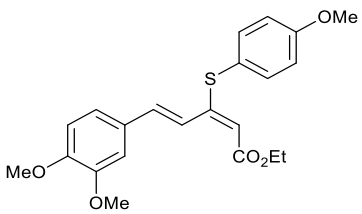
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(*o*-tolylthio)penta-2,4-dienoate (100ic)



General procedure D was followed to yield product **100ic** as a yellow solid (20.4 mg, 0.05 mmol, 75%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.36 (5:1 hexane/ethyl acetate); Mp 78-82 °C ($CDCl_3$); ν_{max}/cm^{-1} 2934 (C-H), 1697 (C=O), 1615 (C=C, diene conj), 1597 (C=C, diene conj), 1581, 1556, 1511 (Ar C-C), 1160 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$), δ 8.26 (1H, dd, *J* = 16.1, 0.8 Hz, CH=C<u>H</u>CS), 7.53 (1H, d, *J* = 7.2 Hz, Ar-H), 7.34-7.41 (3H, m, Ar-H + C<u>H</u>=CHCS), 7.25-7.29 (1H, m, Ar-H), 7.10-7.17 (2H, m, Ar-H), 6.86 (1H, d, *J* = 8.3 Hz, Ar-H), 5.05 (1H, app. s, SC=C<u>H</u>), 4.11 (2H, q, *J* = 7.1 Hz, OCH_2), 3.94 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 2.44 (3H, s, $ArCH_3$), 1.23 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.5 (C), 155.0 (C), 150.1 (C), 149.2 (C), 143.0 (C), 136.8 (CH), 135.8 (CH), 131.2 (CH), 130. 3 (CH), 129.3 (C), 128.9 (C), 127.3 (CH), 122.2 (CH), 121.5 (CH), 111.1 (CH), 110.9 (CH), 109.7 (CH), 59.8 (CH_2), 56.0 (CH_3), 20.5 (CH_3), 14.4 (CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 385.1470, $C_{22}H_{24}O_4S$ requires 385.1468.

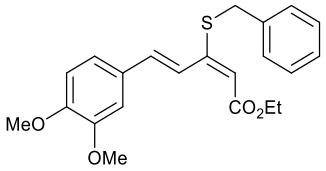
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(4-methoxyphenylthio)penta-2,4-dienoate (100jc)



General procedure D was followed to yield product **100jc** as a yellow solid (14.5 mg, 0.04 mmol, 52%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.20 (5:1 hexane/ethyl acetate); Mp 127-130 °C ($CDCl_3$); ν_{max}/cm^{-1} 2935 (C-H), 1695 (C=O), 1615 (C=C, diene conj), 1590, 1556, 1511 (Ar C-C), 1174 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.22 (1H, dd, *J* = 16.2, 0.9 Hz, CH=C<u>H</u>CS), 7.46 (2H, d, *J* = 8.9 Hz, Ar-H), 7.36 (1H, d, *J* = 16.2 Hz, C<u>H</u>=CHCS), 7.15-7.10 (2H, m, Ar-H), 6.97 (2H, d, *J* = 8.9 Hz, Ar-H), 6.85 (1H, d, *J* = 9.1 Hz, Ar-H), 5.17 (1H, app. s, SC=C<u>H</u>), 4.11 (2H, q, *J* = 7.1 Hz, OCH_2), 3.94 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 1.24 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.6 (C), 161.0 (C), 157.3 (C), 150.2 (C), 149.1 (C), 137.4 (CH), 135.5 (CH), 129.3 (C), 122.1 (CH), 121.4 (CH), 120.0 (C), 115.5 (CH), 111.3 (CH), 111.1 (CH), 109.8 (CH), 59.9 (CH_2), 56.1 (2 x CH_3), 55.3 (CH_3), 14.3 (CH_3); Found (FTMS+ p NSI) [M + H]+ 401.1417, $C_{22}H_{25}O_5S$ requires 401.1417.

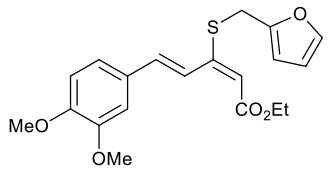
(2*E*, 4*E*)-Ethyl 3-(benzylthio)-5-(3,4-dimethoxyphenyl)penta-2,4-dienoate (100kc)



General procedure D was followed to yield product **100kc** as a yellow solid (13.1 mg, 0.03 mmol, 49%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.29 (5:1 hexane/ethyl acetate); Mp: 99-102 °C ($CDCl_3$); ν_{max}/cm^{-1} 2934 (C-H), 1697 (C=O), 1616 (C=C, diene conj), 1597 (C=C, diene conj), 1581, 1553, 1511 (Ar C-C), 1177 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.19 (1H, dd, *J* = 16.2, 0.9 Hz, CH=C<u>H</u>CS), 7.28-7.41 (5H, m, Ar-H), 7.21 (1H, d, *J* = 16.2 Hz, C<u>H</u>=CHCS), 7.05-7.10 (2H, m, Ar-H), 6.83 (1H, d, *J* = 8.3 Hz, Ar-H), 5.69 (1H, app. s, SC=C<u>H</u>), 4.19 (2H, q, *J* = 7.1 Hz, OCH_2), 4.09 (2H, s, S<u>C</u>H_2Ph), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 1.31 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.2 (C), 155.1 (C), 150.1 (C), 149.1 (C), 135.9 (C), 135.2 (CH), 129.3 (C), 129.1 (CH), 128.8 (CH), 127.7 (CH), 122.3 (CH), 121.5 (CH), 111.1 (CH), 110.4 (CH), 109.7 (CH), 59.9 (CH_2), 55.94 (CH_3), 55.91 (CH_3), 36.8 (CH_2), 14.4 (CH_3); Found (FTMS+ p NSI) [M + H]+ 385.1469, $C_{22}H_{25}O_4S$ requires 385.1468.

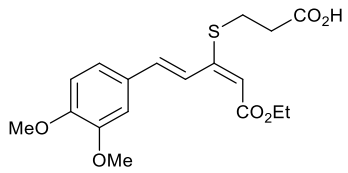
(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(furan-2-ylmethylthio)penta-2,4-dienoate (100lc)



General procedure D was followed to yield product **100lc** as a yellow oil (13.5 mg, 0.04 mmol, 52%). Purified by column chromatography (eulent: hexane/ethyl acetate 5:1).

R_f 0.27 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2935 (C-H), 1697 (C=O), 1581 (C=C, diene conj), 1555, 1511 (Ar C-C), 1177 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.18 (1H, dd, *J* = 16.2, 0.7 Hz, CH=C<u>H</u>CS), 7.38 (1H, dd, *J* = 1.8, 0.8 Hz, Ar-H), 7.21 (1H, d, *J* = 16.2 Hz, C<u>H</u>=CHCS), 7.04-7.12 (2H, m, Ar-H), 6.84 (1H, d, *J* = 8.3 Hz, furan-H), 6.27-6.35 (2H, m, furan-H), 5.73 (1H, app. s, SC=C<u>H</u>), 4.20 (2H, q, *J* = 7.1 Hz, OCH_2), 4.11 (2H, s, SCH_2), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 1.31 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.2 (C), 154.0 (C), 150.1 (C), 149.1 (C), 149.0 (C), 142.6 (CH), 136.3 (CH), 129.2 (C), 122.3 (CH), 121.5 (CH), 111.3 (CH), 111.1 (CH), 110.7 (CH), 109.7 (CH), 108.6 (CH), 60.1 (CH_2), 55.94 (CH_3), 55.91 (CH_3), 29.2 (CH_2), 14.4 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 375.1258, $C_{20}H_{23}O_5S$ requires 375.1261.

(2*E*, 4*E*)-Ethyl 5-(3,4-dimethoxyphenyl)-3-(3-ethoxy-3-oxopropylthio)penta-2,4-dienoate (100mc)

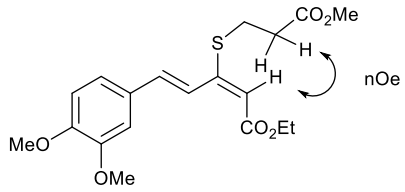


General procedure D was followed to yield product **100mc** as a yellow oil (11.2 mg, 0.03 mmol, 40%). Purified by column chromatography (eluent: ether).

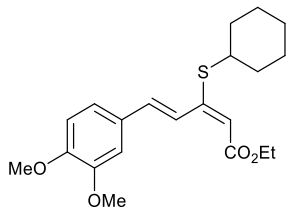
R_f 0.18 (1:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2934 br (O-H), 1700 (C=O), 1616 (C=C, diene conj), 1581 (C=C, diene conj), 1553, 1511 (Ar C-C), 1178 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.19 (1H, dd, *J* = 16.2, 0.7 Hz, CH=C<u>H</u>CS), 7.20 (1H, d, *J* = 16.2 Hz, C<u>H</u>=CHCS), 7.04-7.13 (2H, m, Ar-H), 6.84 (1H, d, *J* = 8.3 Hz, Ar-H), 5.65 (1H, app. s, SC=C<u>H</u>), 4.20 (2H, q, *J* = 7.1 Hz, OCH_2), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.14

(2H, t, *J* = 7.1 Hz $CH_2C\underline{H}_2$), 2.79 (2H, t, *J* = 7.1 Hz, $C\underline{H}_2CH_2$), 1.32 (3H, t, *J* = 7.1 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 176.1 (C), 165.2 (C), 153.6 (C), 150.2 (C), 149.1 (C), 136.4 (CH), 129.2 (C), 122.3 (CH), 121.6 (CH), 111.1 (CH), 110.8 (CH), 109.7 (CH), 60.0 (CH_2), 55.95 (CH_3), 55.92 (CH_3), 32.7 (CH_2), 26.2 (CH_2), 14.4 (CH_3); Found (FTMS+ p NSI) $[M + H]^+$ 365.1057, $C_{18}H_{21}O_6S$ requires 365.1064.

E, *E* stereochemistry confirmed by NOESY δ 5.65 and 3.14



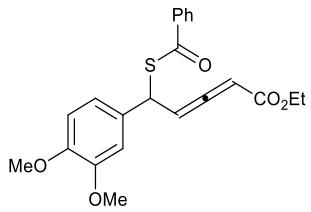
(2*E*, 4*E*)-Ethyl 3-(cyclohexylthio)-5-(3,4-dimethoxyphenyl)penta-2,4-dienoate (100nc)



General procedure D was followed to yield product **100nc** as a yellow oil (12 mg, 0.03 mmol, 45%). Purified by column chromatography (eluent: hexane/ethyl acetate 7:1).

R_f 0.4 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1} 2929 (C-H), 1797 (C=O), 1616 (C=C, diene conj), 1597 (C=C, diene conj), 1580, 1550, 1511 (Ar C-C), 1178 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$), δ 8.19 (1H, dd, *J* = 16.1, 0.8 Hz, CH=C$\underline{H}$CS), 7.25 (1H, d, *J* = 16.1 Hz, C$\underline{H}$=CHCS), 7.05-7.13 (2H, m, Ar-H), 6.84 (1H, d, *J* = 8.3 Hz, Ar-H), 5.71 (1H, app. s, SC=C$\underline{H}$), 4.19 (2H, q, *J* = 7.1 Hz, OCH_2), 3.92 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.14-3.25 (1H, m, alkyl H), 2.02-2.14 (2H, m, alkyl H), 1.76-1.86 (2H, m, alkyl H), 1.60-1.70 (1H, m, alkyl H), 1.37-1.54 (5H, m, alkyl H), 1.26-1.36 (3H, m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 165.5 (C), 154.0 (C), 150.0 (C), 149.1 (C), 136.1 (CH), 129.5 (C), 123.1 (CH), 121.4 (CH), 111.4 (CH), 111.1 (CH), 109.7 (CH), 59.9 (CH_2), 55.94 (CH_3), 55.91 (CH_3), 44.0 (CH), 32.7 (CH_2), 26.0 (CH_2) 25.9 (CH_2), 14.5 (CH_3); Found (FTMS+ p APCI) $[M + H]^+$ 377.1774, $C_{21}H_{29}O_4S$ requires 377.1781.

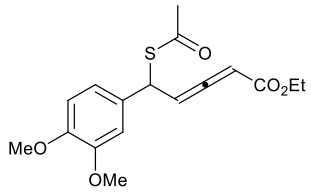
Ethyl 5-(benzoylthio)-5-(2,4-dimethoxyphenyl)penta-2,3-dienoate (116oc)



General procedure D was followed to yield product **116oc** as a yellow oil and as a mixture of diastereomers in a 1:1.9 ratio (18 mg, 0.05 mmol, 66%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.19 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1}, 3061 (C-H), 2979 (C-H), 1963 (C=C, allene), 1712 (C=O), 1661 (C=O), 1591, 1580, 1513, (Ar C-C), 1215 (C-O-C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.90 (2H + 2H', m, Ar-H), 7.45-7.53 (1H + 1H', m, Ar-H), 7.33-7.41 (2H + 2H', m, Ar-H), 6.86-6.90 (2H + 2H', m, Ar-H), 6.72-6.79 (1H + 1H', m, Ar-H), 5.99-6.07 (1H + 1H', m, SCHC<u>H</u>=C=CH), 5.68 (1H', dd, *J* = 5.1, 3.0 Hz, SCHCH=C=C<u>H</u>, minor), 5.62 (1H, dd, *J* = 6.0, 3.1 Hz, SCHCH=C=C<u>H</u>, major), 5.43-5.49 (1H + 1H', m, SC<u>H</u>CH=C=CH, confirmed by NOESY), 4.03-4.13 (2H + 2H', m, OCH_2), 3.84 (3H', s, OCH_3, minor), 3.81 (3H, s, OCH_3, major), 3.78 (3H + 3H', s, OCH_3), 1.14-1.23 (3H + 3H', m, CH_3); ^{13}C NMR ($CDCl_3$, 75.5 MHz), δ 213.0 (C, major), 212.6 (C, minor), 190.3 (C, major), 190.1 (C, minor), 165.3 (C, minor), 165.2 (C, major), 149.1 (C, minor), 148.9 (C, major), 148.8 (C, major + minor), 136.5 (C, major + minor), 133.7 (CH, major + minor), 131.1 (C, minor), 130.7 (C, major), 128.7 (CH, major + minor), 127.3 (CH, major + minor), 120.5 (CH, minor), 120.4 (CH, major), 111.5 (CH, minor), 111.3 (CH, major), 111.1 (CH, minor), 110.9 (CH, major), 98.1 (CH, major + minor), 91.7 (CH, minor), 91.4 (CH, major), 61.0 (CH_2, major + minor), 56.0 (CH_3, minor), 55.9 (CH_3, minor), 55.89 (CH_3, major), 55.87 (CH_3, major), 45.8 (CH, major), 45.2 (CH, minor), 14.2 (CH_3, major + minor); Found (FTMS+ p NSI) $[M + H]^+$ 399.1255, $C_{22}H_{23}O_5S$ requires 399.1261.

Ethyl 5-(acetylthio)-5-(3,4-dimethoxyphenyl)penta-2,3-dienoate (116pc)



General procedure D was followed to yield product **116pc** as a yellow oil as a mixture of diastereomers in a 1:0.7 ratio (10.5 mg, 0.03 mmol, 52%). Purified by column chromatography (eluent: hexane/ethyl acetate 5:1).

R_f 0.23 (5:1 hexane/ethyl acetate); ν_{max}/cm^{-1}, 3061 (C-H), 2980 (C-H), 1963 (C=C, allene), 1692 (C=O), 1661 (C=O), 1590, 1513, (Ar C-C), 1215 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.87-7.00 (2H + 2H', m, Ar-H), 6.75-6.83 (1H + 1H', m, Ar-H), 5.98 (1H + 1H', m, SCHC<u>H</u>=C=CH), 5.75 (1H', dd, *J* = 6.1, 3.1 Hz, SCHCH=C=C<u>H</u>, minor), 5.66 (1H, dd, *J* = 6.1, 3.1 Hz, SCHCH=C=C<u>H</u>, major), 5.27-5.34 (1H + 1H', m, SC<u>H</u>), 4.13-4.24 (2H + 2H', m, OCH_2), 3.89 (3H', s, OCH_3, minor), 3.86 (6H + 3H', s, OCH_3), 2.33 (3H, s, O=CCH_3, major), 2.32 (3H', s, O=CCH_3, minor), 1.23-1.33 (3H + 3H', m, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 212.9 (C, major), 212.4 (C, minor), 194.1 (C, major), 193.8 (C, minor), 165.3 (C, minor), 165.2 (C, major), 149.0 (C, minor), 148.9 (C, major), 148.77 (C, minor), 148.76 (C, major), 131.2 (C, minor), 130.7 (C, major), 120.3 (CH, minor), 120.2 (CH, major), 111.3 (CH, minor), 111.2 (CH, major), 111.0 (CH, minor), 110.9 (CH, major), 98.02 (CH, major), 97.86 (CH, minor), 91.6 (CH, minor), 91.3 (CH, major), 61.0 (CH_2, major + minor), 56.0 (CH_3, minor), 55.9 (CH_3, minor), 55.88 (CH_3, major), 55.85 (CH_3, major), 45.7 (CH, major), 45.1 (CH, minor), 30.33 (CH_3, major), 30.28 (CH_3, minor), 14.2 (CH_3, major + minor); Found (FTMS+ p NSI) $[M + NH_4]^+$ 354.1369, $C_{17}H_{24}NO_5S$ requires 354.1370.

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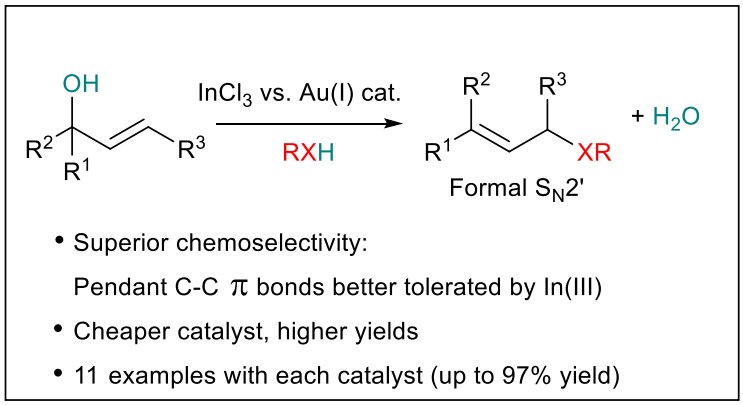
Chapter 3: Indium *vs* Gold Catalysis in Dehydrative Reactions with Allylic Alcohols



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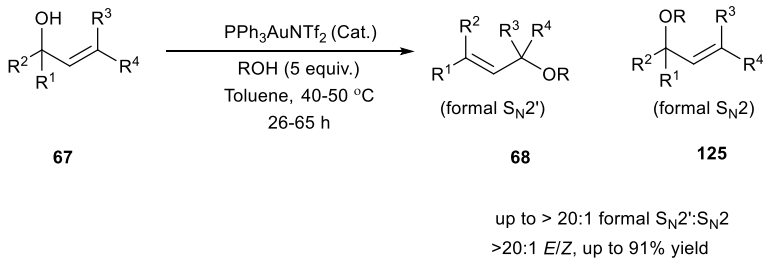
I would like to thank Louise Schaefer (MChem Student) for her optimisation studies on substrates **130** and **156** and for the initial small scale reactions of product **150**.

3.1 Introduction

It was discussed in Chapter 2 that $InCl_3$ is a much more effective catalyst for the dehydrative reaction of allenols with thiols compared to Au(I). Therefore, at the outset of this project we aimed to re-investigate the dehydrative reaction of allylic alcohols by comparing In(III) and Au(I) catalysts. Thus, a brief introduction to the initial gold(I)-catalysed dehydrative reactions of allylic alcohols by the Lee group will be discussed.

Allylic alcohols can react with a wide range of nucleophiles in the presence of transition metal complexes, including but not limited to Pd(0),[1] Pt(II),[2] Bi(III),[3] Ir(II),[4] Mo(VI), Au(I) and Au(III).[5] However, unlike gold, some of these transition metal complexes are air and moisture sensitive and therefore the use of gold is preferred.

Substitution of the allylic alcohol by a nucleophile usually requires preactivation of the alcohol to form a better leaving group such as a halide, carboxylate, phosphate, or carbonate.[6] However, Lee and co-workers developed a gold(I)-catalysed reaction which does not require strong bases, inert conditions or preactivation of the alcohol, thus increasing substrate scope (Scheme 3.1).[7] The group found that the intermolecular direct allylic etherification of unactivated alcohols not only occurs with good yields but is also regioselective (formal S_N2'), stereoselective (*E*) and tolerates a wide range of substrates including primary, secondary and tertiary allylic alcohols and alcohol nucleophiles.

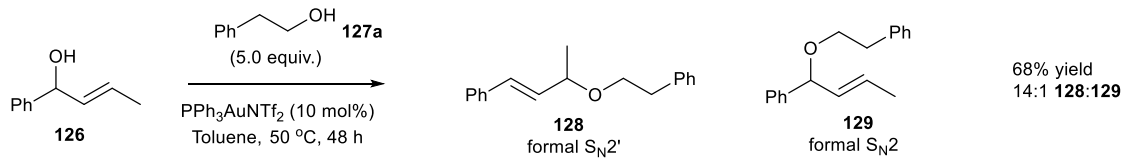


Scheme 3.1: Gold(I)-catalysed reaction of allylic alcohols with alcohol nucleophiles

With tertiary allylic alcohols and primary alcohol nucleophiles, the group found that the reaction was regioselective and stereoselective where, in most cases, only the formal S_N2' product was formed with an *E*/*Z* ratio greater than 20:1 respectively. These reactions were also able to tolerate a wide range of functional groups including isolated alkenes, electrophilic alkyl chlorides, acid-sensitive acetals and esters which would not have been tolerated under the previous conditions. The group reported yields upwards of 65%.

Indeed, this also stands when the steric hindrance of the alcohol nucleophile was increased to include secondary alcohols. When the sterics were increased further to include tertiary alcohol nucleophiles, a good yield was still obtained (57%).[7]

Although the reaction remained high yielding with secondary allylic alcohols, the reaction was less regioselective and often resulted in poorer ratios of the formal S_N2' and formal S_N2 products (Scheme 3.2).[7]



Scheme 3.2: Reaction of secondary allylic alcohols

As described previously, the reaction tolerated a wide range of nucleophiles including an alcohol containing a pendent alkene **127b** (Figure 3.1). However, when alcohols containing pendent alkynes **127c** were investigated, a complex mixture of products was observed. This is also the case when allylic alcohols containing pendent alkenes **130** were investigated as substrates. Furthermore, Au(I)-catalysts are not tolerant of alcohol nucleophiles containing amines **127d** and **127e**. Therefore, a catalyst or improved conditions which are tolerant of these functional groups is desired.

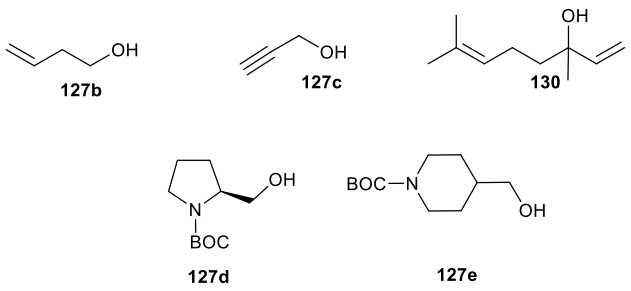
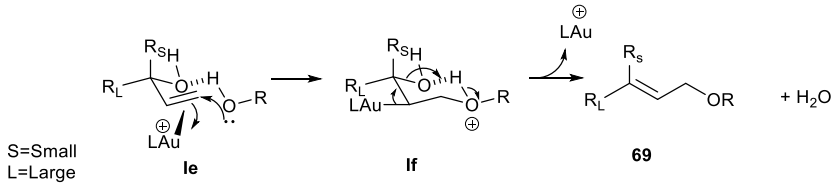


Figure 3.1: Functional groups

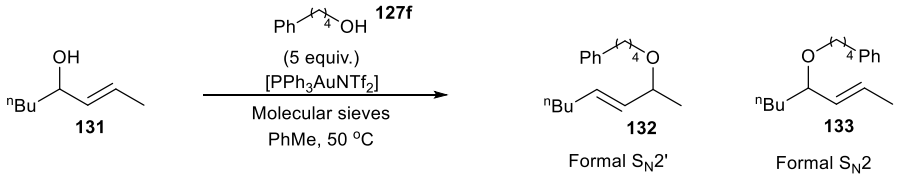
The group proposed a mechanism whereby the transition state is a chair-like 6-membered ring (Scheme 3.3). The gold catalyst activates the alkene towards a nucleophilic attack (**Ie**) which is then followed by demetallation and elimination of water (**If**) (possibly enabled by hydrogen bonding) to regenerate the catalyst and produce the desired allylic ether **69**.[7]



Scheme 3.3: Allylic alcohol mechanism for the gold(I) catalysed direct etherification of allylic alcohols

The proposed mechanism *via* a chair-like transitions state suggests the reaction should proceed with chirality transfer. To provide evidence for the proposed mechanism, computational and experimental investigations on enantioenriched allylic alcohols were carried out in collaboration with the Macgregor group.

Initial investigations commenced with optimisation of the reaction conditions for secondary allylic alcohols. As previously reported, the use of secondary allylic alcohols as substrates often resulted in poor regioselectivity, 2.5:1 **132**:**133** (Scheme 3.4). However, by adding molecular sieves and portion-wise addition of the Au(I) catalyst, excellent regioselectivities were observed, >20:1 **132**:**133** (Scheme 3.4).[8]

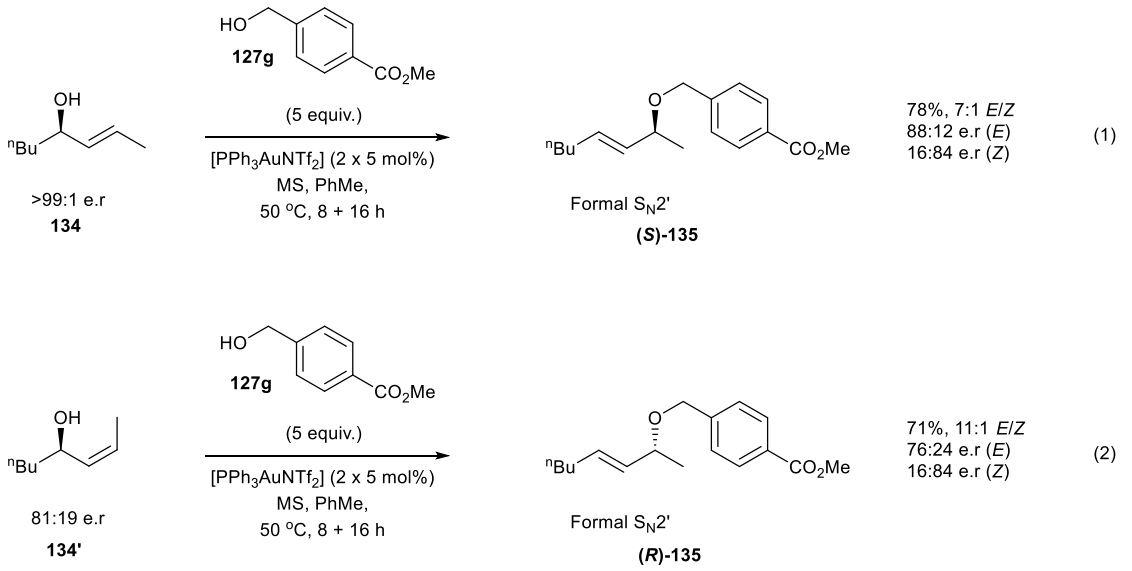


1. 10 mol% Au(I), 48 h, **no molecular sieves**, 62%, 2:1 **132**:**133**, 10:1 *E*/*Z*

2. 2 x 5 mol% Au(I), 8 + 16 h, **molecular sieves**, 84%, >20:1 **132**:**133**, 7:1 *E*/*Z*

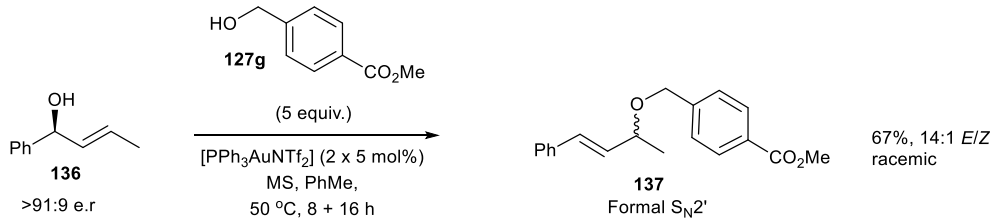
Scheme 3.4: Initial optimisation of secondary allylic alcohols

With the optimised conditions in hand, Lee and co-workers turned their attention to the chirality transfer reaction. Enantioenriched *E*-allylic alcohol **134** gave the desired product **135** in 88:12 e.r from >99:1 e.r of starting material **134**. The minor *Z* isomer was obtained in 84:16 e.r (Scheme 3.5, Eq. 1). The opposite enantiomer of the product could be obtained with good chirality transfer by starting with the *Z*- allylic alcohol **134'** (Scheme 3.5, Eq. 2). The reaction is therefore stereospecific.



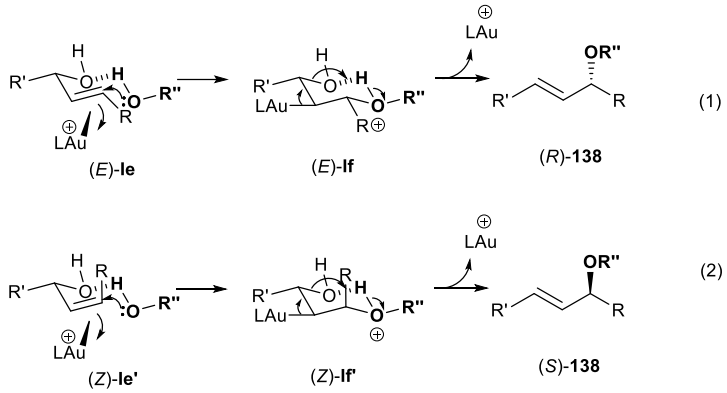
Scheme 3.5: Chirality transfer with enantioenriched allylic alcohols

However, when the group attempted chiral transfer with allylic alcohols containing phenyl substituents, the products were racemic (Scheme 3.6).



Scheme 3.6: Racemisation of products from enantioenriched Ph-substituted allylic alcohols

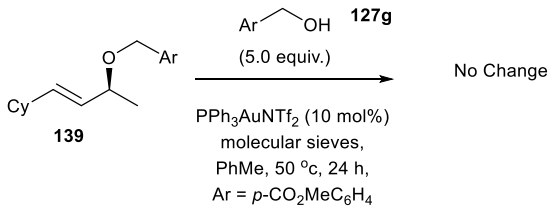
The mechanism that the group originally proposed for the allylic etherification reaction can account for the chirality transfer and the stereospecificity of the reaction (Scheme 3.7). The *E* isomer has its substituent, R, in the equatorial position and therefore produces the (*R*)-enantiomer (Scheme 3.7, Eq. 1). However, as stated previously the *Z* isomer gives the opposite (*S*)-enantiomer as its substituent, R, is in the axial position (Scheme 3.7, Eq. 2).



Scheme 3.7: Proposed mechanism for chirality transfer

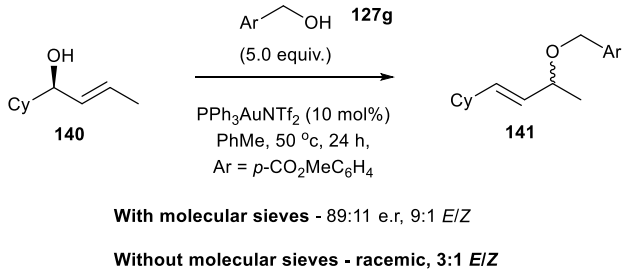
From the proposed mechanism, it is shown that the hydrogen-bonded 6-membered transition state **Ie** is essential for chirality transfer. Thus, any erosion of the *ee* could be due to disruption of hydrogen bonding in this transition state. A second possibility for the erosion of *ee* could be due to racemisation of product **138** through isomerisation of formal S_N2' and formal S_N2 products. In order to provide evidence that the latter is not occurring, Lee and co-workers carried out several control reactions.

The enantioenriched formal S_N2' product **139** was resubjected to the original reaction conditions. If isomerisation was indeed occurring, the products obtained would be racemic. However, this was not observed, suggesting that any erosion of *ee* was not caused by isomerisation of the formal S_N2' products (Scheme 3.8).



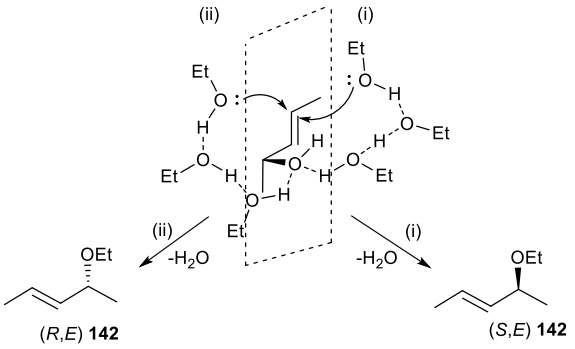
Scheme 3.8: Resubjection of enantioenriched projects to reaction conditions

Their next control reaction showed that molecular sieves are crucial for chirality transfer and good *E*/*Z* selectivity. Without molecular sieves, complete racemisation of the product occurs (Scheme 3.9).



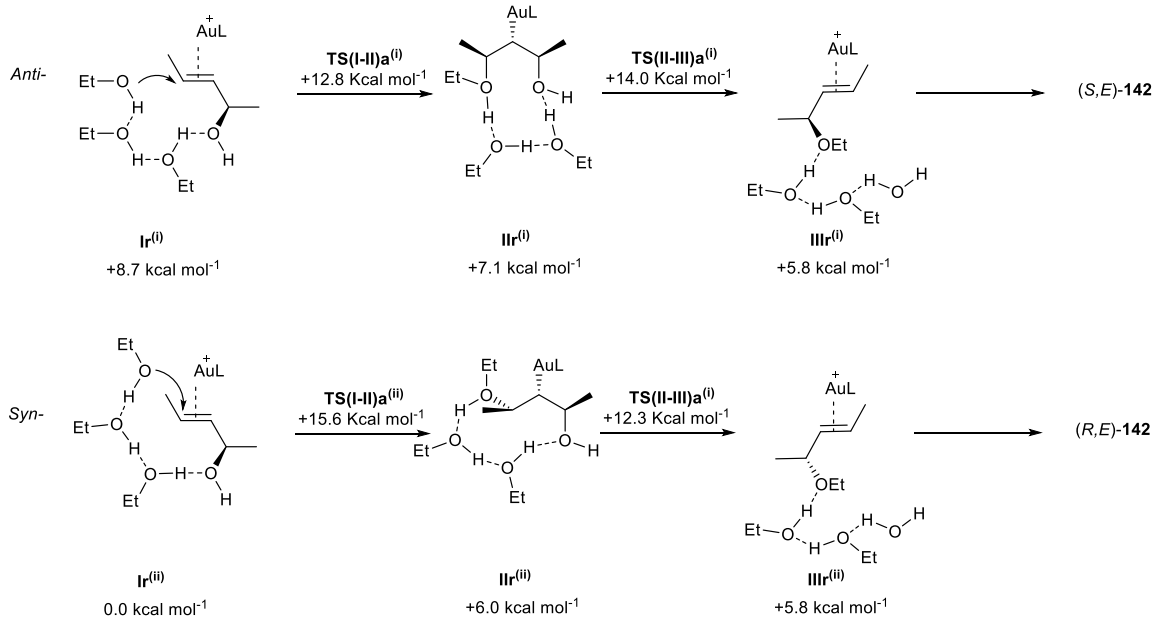
Scheme 3.9: Allylic etherification without molecular sieves

With this in mind, computational studies were carried out in order to establish why a loss in chirality transfer occurs when molecular sieves were not present in the reaction. The group proposed a mechanism involving nucleophilic attack at one face of the allylic alcohol and loss of water from the opposite face by invoking a proton chain transfer mechanism with several EtOH molecules (Scheme 3.10).



Scheme 3.10: Possible mechanism accounting for loss of chirality transfer

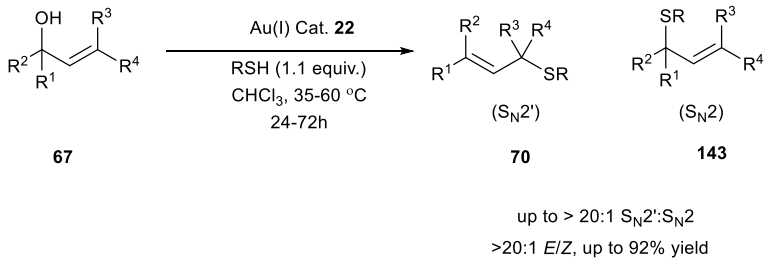
Pathway (i) involves an *anti*- attack by EtOH, where a 3 EtOH molecule chain promotes the loss of water *anti*- to Au(I) forming (*S*,*E*)-**142**. Whereas pathway (ii) involves *syn*-attack by EtOH but the loss of water still occurs *anti*- to Au(I) due to the proton chain.



Scheme 3.11: key intermediates

The most stable hydrogen bonded precursor has the EtOH positioned over the Au centre **Ir$^{(ii)}$**, which leads to the (*R*,*E*)-**142** product *via* pathway (ii) (Scheme 3.11). The alternative pathway (i) starts with the precursor **Ir$^{(i)}$** which is 8.7 Kcal mol^{-1} higher in energy and leads to the (*S*,*E*)-**142** product. Similar barrier heights were observed for the formation of both products (ΔG = 14.0 and 15.6 Kcal mol^{-1} respectively) and accounts for the racemisation observed during experimental work when no molecular sieves are added to the reaction. The group proposed that when molecular sieves are added to the reaction they disrupt the proton chain transfer mechanism and promote chirality transfer.[8]

Having successfully developed the reaction of allylic alcohols with alcohol nucleophiles, the Lee group have recently expanded the nucleophile scope to include thiols (Scheme 3.12).

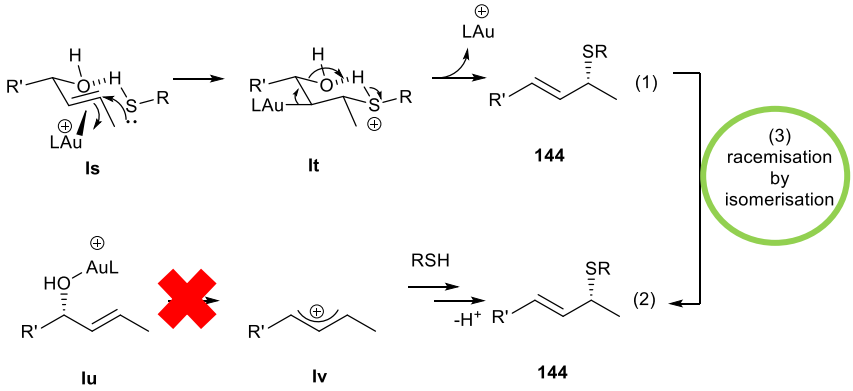


Scheme 3.12: Gold(I) catalysed reaction of allylic alcohols with sulfur nucleophiles

The reaction was found to have a wide substrate scope including primary, secondary and tertiary allylic alcohols and tolerated a wide range of substituents on the thiol nucleophile. Although the reaction was shown to tolerate a wide range of substrates, no investigations were carried out using allylic alcohols containing pendent alkenes or alkynes (Figure 3.1). Therefore, further investigation into the chemoselectivity of the reaction is required.

The group then attempted to extend this methodology to asymmetric catalysis *via* chirality transfer but only racemic products were obtained, suggesting that the factors controlling allylic etherification and allylic thioetherification could be different. Adding molecular sieves to the reaction was also detrimental to the thioetherification with no product being formed.

To account for this, the group proposed the following mechanistic pathways (scheme 3.13).

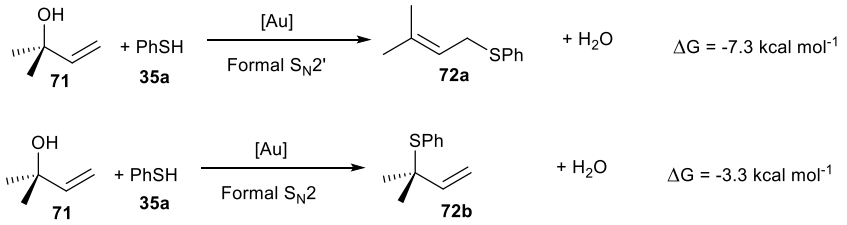


Scheme 3.13: Plausible mechanistic pathways.

Pathway one is a similar mechanism to that proposed for allylic etherification and once again the chair-like 6-membered ring transition state **Is** is crucial for chirality transfer. Pathway two is an alternative mechanism which would explain the racemisation as the reaction proceeds through an allyl cation **Iv**. If the reaction does proceed *via* pathway two then poor regioselectivities would have been expected. However, a good 8:1 formal S_N2'/S_N2 ratio is observed. Therefore, a third alternative pathway was considered whereby the reaction proceeds *via* pathway one but then racemises *via* isomerisation of the formal S_N2' and S_N2 products (Scheme 3.13).

In order to shed light on the potential mechanisms involved, computational studies were carried out in collaboration with the Macgregor group. The initial investigations focused on the thermodynamic stabilities of the formal S_N2' and S_N2 products. It was found that

the formal S_N2' product **72a** was 4.0 Kcal mol^{-1} more stable than the formal S_N2 **72b** (Scheme 3.14).



Scheme 3.14: Computed thermodynamic stability of products

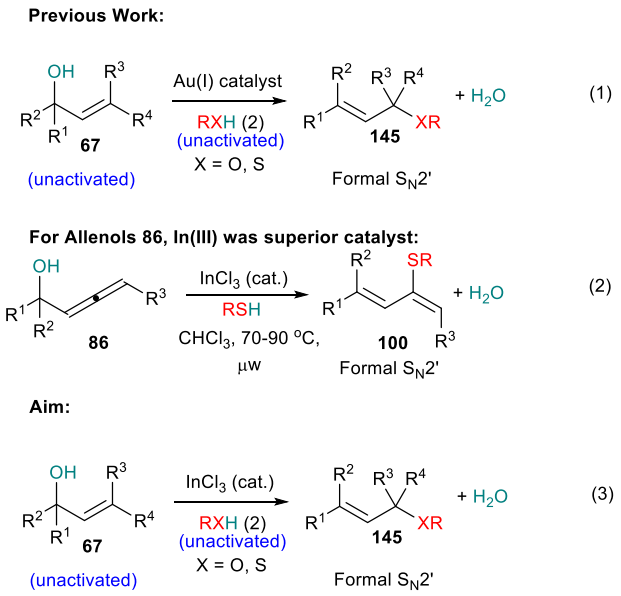
However, the formal S_N2' product can either be released or continue to do a further S_N2' step to produce the formal S_N2 product. This route to the formal S_N2 product is kinetically favoured over a direct S_N2 reaction.

Computational studies also investigated the formation of an allylic cation but found that the process is endergonic and therefore unlikely. This suggests that the loss of chirality transfer does not arise from isomerisation *via* pathway two as shown in Scheme 3.13. They found that the computational investigations point towards accessible isomerisations between the formal S_N2' and S_N2 products. Thus, the proposed mechanistic pathway proceeds *via* pathway 1 followed by isomerisation of the products *via* pathway 3 (Scheme 3.13).[9]

In summary, dehydrative etherification and thioetherification of allylic alcohols proceeds well under Au(I) catalysis. However, initial studies showed that substrates or nucleophiles containing pendent alkenes or alkynes are not tolerated. Dehydrative etherification of allylic alcohols proceeds with good chirality transfer (as long as molecular sieves are added to the reaction) but thioetherification results in racemic products. This suggests slightly different mechanisms may be in operation in both reactions.

3.2 Project Aims

In recent years the Lee group has developed intermolecular etherification and thioetherification reactions with allylic alcohols (Scheme 3.15, Eq. 1). These reactions were highly regioselective for the formal S_N2' product and, as discussed in section 3.1, could be carried out without activation of either the allylic alcohol or the incoming nucleophile, leaving only water as the by-product. The group then hoped to extend this chemistry by applying this concept to allenols (Scheme 3.15, Eq. 2). However, as discussed in chapter 2, the gold catalyst produced a complex mixture of products and, as a result, a soft Lewis acid screen was carried out. It was found that $InCl_3$ was an excellent catalyst for dehydrative reactions with allenols.



Scheme 3.15: Previous work Eq. 1 and 2 and current aim Eq. 3

Since $InCl_3$ is a cheaper catalyst than Au(I) and is also tolerant of air and moisture as well as being non-toxic, we decided to investigate $InCl_3$ as an alternative catalyst to Au(I) with allylic alcohol substrates (Scheme 3.15, Eq. 3). In particular, we intended to focus on substrates which were low yielding or provided a complex mixture of products under the original Au(I)-catalysis conditions.

3.3 Results and discussion

Under initial reaction conditions with gold(I), allylic alcohol **146** containing an electron-rich aryl produced a complex mixture of products. Therefore, initial investigations with $InCl_3$ began with this substrate (Table 3.1). It should be noted that the choice of Au(I) catalyst is derived from previously optimised conditions, with PPh_3AuNTf_2 acting as the most effective catalyst when using alcohol nucleophiles and Au(I) catalyst **22** (Echavarren catalyst) when using thiols.

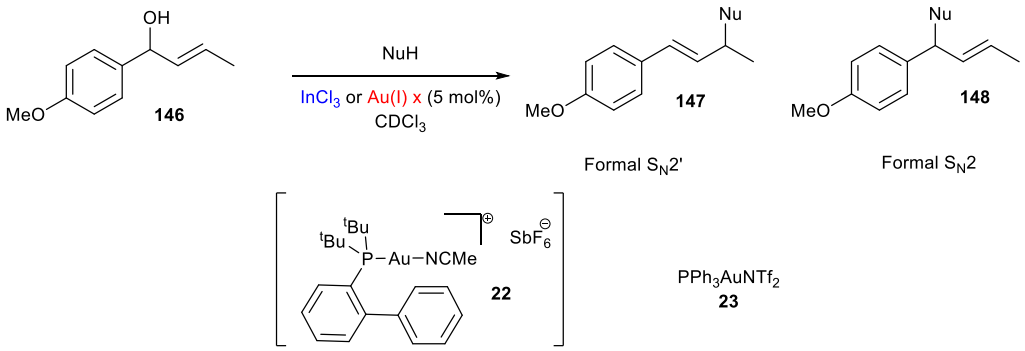
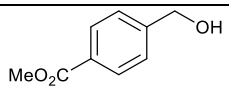
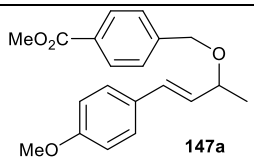
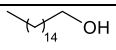
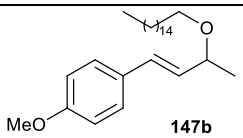
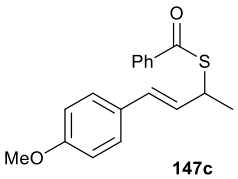
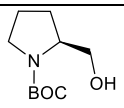
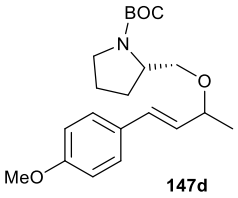
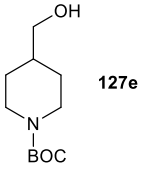
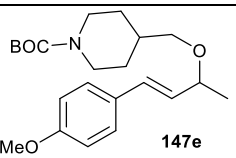
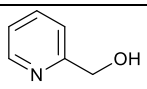
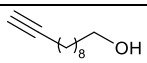
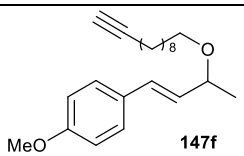


Table 3.1: Nucleophile Scope

Entry	Nucleophile[a]	Cat.	Temp (°C)	Time (mins)	Product	Yield[b] (%) **147**:**148**	*E*/*Z*
1	 **127g**	$InCl_3$	30	30	 **147a**	77 >20:1	>20:1
2		Au(I) cat **23**	30	30		67 >20:1	>20:1
3	 **127h**	$InCl_3$	30	30	 **147b**	62 >20:1	>20:1
4		Au(I) cat **23**	30	30		55 >20:1	>20:1
5	 **35o**	$InCl_3$	30	60	 **147c**	85 >20:1	>20:1
6		Au(I) cat **22**	30	60		78 >20:1	>20:1

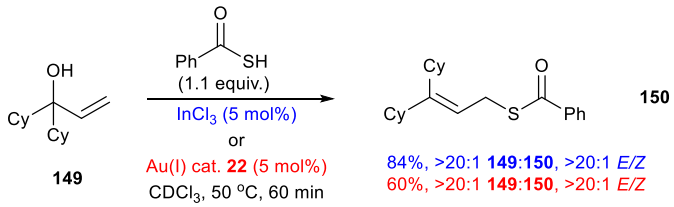
7	 **127d**	$InCl_3$	30	30	 **147d**	90 >20:1	>20:1
8		Au(I) cat **23**	30	30		53 >20:1	>20:1
9	 **127e**	$InCl_3$	30	30	 **147e**	72 >20:1	>20:1
10		Au(I) cat **23**	30	30		71 >20:1	>20:1
11	 **127i**	$InCl_3$	30	30	No reaction	N/A	N/A
12		Au(I) cat **23**	30	30	No reaction	N/A	N/A
13	 **127j**	$InCl_3$	30	30	 **147f**	79 >20:1	>20:1
14		Au(I) cat **23**	30	30	Complex mixture of products	N/A	N/A

[a]Alcohol nucleophile – 5.0 equiv., Thiol nucleophile – 1.1 equiv. [b]Isolated yields.

We were pleased to find that lowering the time and temperature of the reaction (30 mins *vs* 24 h and 50 °C *vs* 30 °C respectively) gave the desired product in good yields using both $InCl_3$ and Au(I) catalysts (entry 1 and 2). This was also the case when nucleophiles **127h** and **35o** were used in the reaction (entries 3-6). In the case of all three nucleophiles, $InCl_3$ performed slightly better than Au(I) with a small increase in yield observed (<10%). However, a significant contrast in yield was observed when *N*-Boc-L-prolinol **127d**, containing a proximal NBoc moiety, was used as a nucleophile. $InCl_3$ outperforms Au(I), producing the desired product in 90% yield (entry 7). In contrast, only a 53% yield is obtained under Au(I) catalysis (entry 8). This may be due to the Au(I) catalyst having a lower tolerance of the proximal NBoc group. Indeed, when the NBoc moiety is moved further from the OH group, both $InCl_3$ and Au(I) perform well (entries 9 and 10). However, when the *N*-lone pair is more available, neither $InCl_3$ nor Au(I) can catalyse the reaction, presumably due to the deactivation of the catalyst (entry 11 and 12). Next an alcohol nucleophile containing a pendent alkyne was investigated to test the

chemoselectivity of the reaction. $InCl_3$ proves to be the far superior catalyst with this particular nucleophile, with no reaction seen at the alkyne. With Au(I), not unexpectedly, the reaction produces a complex mixture of products, presumably due to reactions with the pendent alkyne.

Next, reactions with tertiary allylic alcohol **149** were investigated (Scheme 3.16). Thioacid **35o** was used as a nucleophile since good yields had been obtained with both $InCl_3$ and Au(I) with allylic alcohol **146**. It was observed that $InCl_3$ again provided an excellent yield of the desired formal S_N2' product (84%), whilst Au(I) yielded only 60% of the desired product. This may be because In(III) catalysts readily tolerate sulfur compared to Au(I) catalysts. These reactions can be carried out on a larger scale (1 mmol *vs* 0.07 mmol) where higher yields were obtained, 97% for the In(III) catalysed reaction and 81% for Au(I).



Scheme 3.16: Tertiary allylic alcohol **149** with thioacid **35o** – In(III) *vs* Au(I)

Next, the chemoselectivity of the reaction was investigated by using allylic alcohols containing pendent alkenes, with 4-nitrothiophenol acting as a nucleophile (Table 3.2).

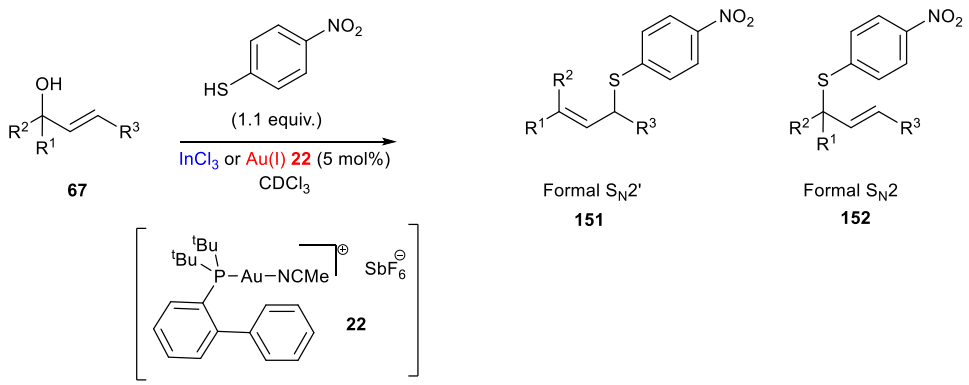
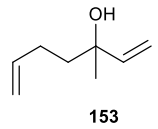
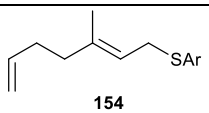
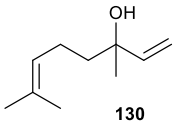
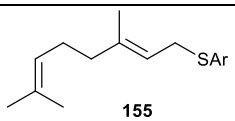
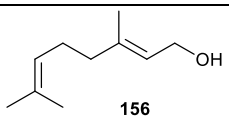
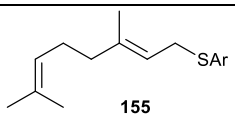


Table 3.2: Allylic alcohol scope.

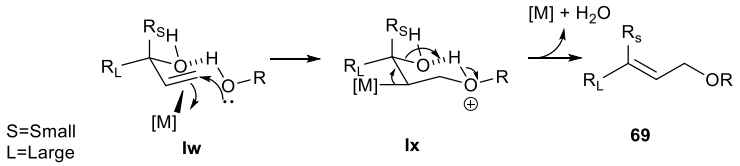
En-try	Allylic alcohol	Cat.	Temp (°C)	Time (mins)	Product	Yield[a] (%)	*E/Z*
1	 **153**	$InCl_3$	80	30	 **154**	48(**154**) ND[b]	>3:1
2		Au(I) cat **22**	80	30	**154** + mixture of unidentified side products	15(**154**) ND[b]	>20:1
3	 **130**	$InCl_3$	50	240	 **155**	31(**155**) 2.5:1	>20:1
4		Au(I) cat **22**	50	240	**155** + mixture of unidentified side products	16(**155**) 2.5:1	>20:1
5	 **156**	$InCl_3$	50	240	 **155**	28(**155**) 3:1	>20:1
6		Au(I) cat **22**	50	240	**155** + mixture of unidentified side products	9(**155**) 6:1	>20:1

[a]Isolated yield. [b]Not determined, overlapping peaks.

In all cases, $InCl_3$ was the most effective catalyst for the reaction. Allylic alcohol **153** containing a pendent monosubstituted alkene, produced the desired product in a 48% yield under $InCl_3$ catalysis (entry 1). However, under the same reaction conditions using Au(I) as a catalyst, only a 15% yield of the desired product was obtained along with a mixture of unidentified side products (entry 2). Next, the related allylic alcohol **130**, commercially available linalool, containing a trisubstituted alkene was investigated.

Again $InCl_3$, performed better than Au(I) albeit with moderate to poor yields, 31% and 16% respectively (entries 3 and 4). Finally, the isomer of linalool, geraniol **156**, was investigated. A complex mixture of products was formed under Au(I) catalysis with only a 9% yield of product **155** being isolated (entry 6), whilst $InCl_3$ gave a slightly better yield of 28% (entry 5). Interestingly, the formal S_N2 product **155** was favoured in this case, which is the same as the formal S_N2' product **155** in entries 5 and 6. This suggests that the selectivity of the reaction is under thermodynamic control as previously described.

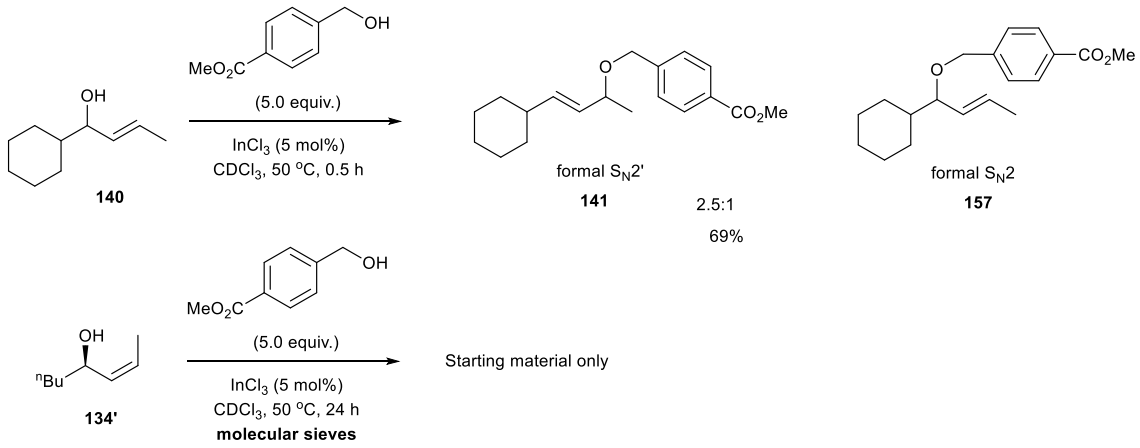
Since $InCl_3$ is a soft Lewis acid, it is possible that the reaction mechanism is similar to the proposed mechanism for Au(I) (Scheme 3.17).



Scheme 3.17: Proposed mechanism

The indium catalyst activates the alkene towards a nucleophilic attack (**Iw**) which is then followed by demetallation and elimination of water (**Ix**) (possibly enabled by hydrogen bonding) to regenerate the catalyst and produce the desired allylic ether **69**.

The Lee group in collaboration with the Macgregor group have recently investigated experimentally and computationally the chirality transfer in gold(I)-catalysed direct allylic etherification of unactivated alcohols.[8] Therefore, an initial attempt was made to investigate chiral transfer using $InCl_3$ as a catalyst (Scheme 3.18).



Scheme 3.18: Chirality transfer

Without molecular sieves, secondary allylic alcohols react efficiently with alcohol nucleophiles to form the desired products **141** and **157** in good yields (69%).[1] However the reaction is not regioselective and produces a mixture of the formal S_N2' and S_N2 products. Next an enantioenriched allylic alcohol was used as a substrate to ascertain whether chirality transfer was possible. Molecular sieves were added as it is shown to improve the regioselectivity and enantioselectivity with gold(I)-catalysis (see section 3.1). However, when molecular sieves were present in the reaction mixture none of the desired products were observed and only starting material was recovered. This suggests that molecular sieves shut down the reaction under $InCl_3$ catalysis.

[1] Carried out by Graeme Barker

3.4 Conclusions

$InCl_3$ provides a cheaper alternative to gold(I) for catalytic dehydrative reactions of allylic alcohols with alcohol and thiol nucleophiles. Indeed, the use of $InCl_3$ as a catalyst resulted in a higher yield of several products compared to the gold(I)-catalysed reaction. This effect was most notable when chemoselectivity was an issue. For example, substrates containing pendent alkenes or alkynes reacted efficiently under In(III) catalysis but produced complex mixtures of products when Au(I) catalysts were used.

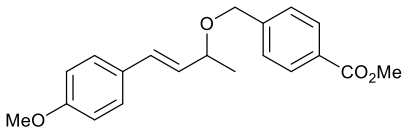
Unfortunately, initial studies show that $InCl_3$ is not efficient in the chirality transfer reaction as the addition of molecular sieves (required for good chirality transfer) seems to shut down the reaction.

Therefore, $InCl_3$ should be considered as an alternative catalyst for dehydrative reactions of allylic alcohols, especially when substrates contain pendent C-C π bonds.

3.5 Experimental

Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks. *J* values are given in Hz and s, bs, d, dd, ddd, dt, t, td, tt, tq, q, qn, sext and m abbreviations correspond to singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublets, doublet of triplets, triplet, triplet of doublets, triplet of triplets, triplet of quartets, quartet, quintet, sextet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained deposited neat or as a chloroform solution to a diamond/ZnSe plate. All allylic alcohols were prepared by known literature procedures. Alcohols and thiols were purchased and used without further purification. $CDCl_3$ and toluene were purchased and used without further purification. Both indium(III) and gold(I)-catalysed reactions were carried out without the need for dry solvents or inert atmosphere, unless stated otherwise. TLC Silica gel 60 F_{254} were used for preparative TLC.

Methyl (*E*)-4-(((4-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)benzoate (147a)



Gold(I) catalysis:

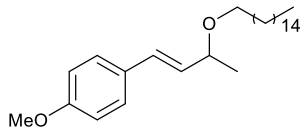
Allylic alcohol **146** (12.4 mg, 0.070 mmol, 1.0 equiv.), alcohol **127g** (56.3 mg, 0.34 mmol, 5.0 equiv.) and PPh_3AuNTf_2 (2:1 toluene adduct) (2.8 mg, 5 mol%) and $CDCl_3$ (0.7 ml) were added to a vial and stirred at 30 °C for 30 mins. The crude mixture was purified by column chromatography (3:1 hexane/ether) to yield product **147a** as colourless oil (67%, 15.2 mg, 0.047 mmol).

$InCl_3$ Catalysis:

A solution of allylic alcohol **146** (12.7 mg, 0.071 mmol, 1 equiv.) in $CDCl_3$ (0.20 ml) was added to a solution of $InCl_3$ (0.9 mg, 5 mol%) and alcohol **127g** (57.0 mg, 0.34 mmol, 5.0 equiv.) in $CDCl_3$ (0.35 ml). The vial containing the allylic alcohol solution was then rinsed with $CDCl_3$ (0.15 ml) and washings added to reaction mixture. The resulting mixture was stirred at 30 °C for 30 mins and then purified by column chromatography (3:1 hexane/ether) to yield product **147a** as a colourless oil (77%, 17.8 mg, 0.055 mmol).

R_f 0.34 (3:1 hexane/ether); IR ν (cm^{-1}) 2951, 2837 (C-H), 1717 (C=O), 1606, 1576, 1510 (C-C Ar), 1247 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (2H, d, *J* = 8.5 Hz, Ar-H), 7.42 (2H, d, *J* = 8.6 Hz, Ar-H), 7.34 (2H, d, *J* = 8.5 Hz, Ar-H), 6.87 (2H, d, *J* = 8.6 Hz, Ar-H), 6.49 (1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CH), 6.01 (1H, dd, *J* = 15.9, 7.9 Hz, ArCH=C<u>H</u>), 4.66 (1H, d, *J* = 12.8 Hz, OC<u>H</u>HAr), 4.49 (1H, d, *J* = 12.8 Hz, OCH<u>H</u>Ar), 4.03-4.11 (1H, m, =CHC<u>H</u>CH_3), 3.91 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 1.40 (3H, d, *J* = 6.3 Hz, CHC<u>H_3</u>); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.2 (C), 159.6 (C), 144.5 (C), 131.4 (CH), 129.8 (CH), 129.4 (C), 129.3 (C), 129.2 (CH), 127.8 (CH), 127.3 (CH), 114.2 (CH), 76.7 (CH), 69.5 (CH_2), 55.5 (CH_3), 52.2 (CH_3), 22.0 (CH_3); Found (*p* NSI) $[M+Na]^+$ 349.1413, $C_{20}H_{22}O_4Na$ requires 349.1410.

(*E*)-1-(3-(Hexadecyloxy)but-1-en-1-yl)-4-methoxybenzoate (147b)



Gold(I) catalysis:

Allylic alcohol **146** (12.2 mg, 0.069 mmol, 1.0 equiv.), alcohol **127h** (79.8 mg, 0.33 mmol, 5.0 equiv.) and PPh_3AuNTf_2 (2:1 toluene adduct) (2.7 mg, 5 mol%) and $CDCl_3$ (0.7 ml) were added to a vial and stirred at 30 °C for 30 mins. The crude mixture was purified by column chromatography (7:1 hexane/ether) to yield product **147b** as white solid (55%, 15.3 mg, 0.038 mmol).

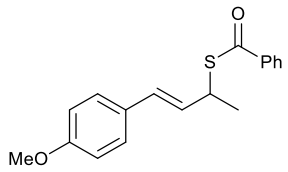
$InCl_3$ Catalysis:

A solution of allylic alcohol **146** (12.3 mg, 0.069 mmol, 1 equiv.) in $CDCl_3$ (0.15 ml) was added to a solution of $InCl_3$ (0.7 mg, 5 mol%) and alcohol **127h** (82.1 mg, 0.34 mmol, 5.0 equiv.) in $CDCl_3$ (0.35 ml). The vial containing the allylic alcohol solution was then rinsed with $CDCl_3$ (0.20 ml) and washings added to reaction mixture. The resulting mixture was stirred at 30 °C for 30 mins and then purified by column chromatography (7:1 hexane/ether) to yield product **147b** as a white solid (62%, 17.2 mg, 0.043 mmol).

R_f 0.63 (3:1 hexane/ether); Mp: 52-53 °C ($CDCl_3$); IR ν (cm^{-1}) 2922, 2852 (C-H), 1608, 1578, 1511 (C-C Ar), 1250 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.5 Hz, Ar-H), 6.86 (2H, d, *J* = 8.5 Hz, Ar-H), 6.45 (1H, d, *J* = 15.9 Hz, ArC<u>H</u>=CH), 5.97 (1H, dd, *J* = 7.6, 15.9 Hz, ArCH=C<u>H</u>), 3.92-3.99 (1H, m, =CHC<u>H</u>CH_3), 3.81 (3H, s,

OCH_3), 3.48 (1H, dt, *J* = 6.9, 9.3Hz, OC<u>H</u>HCH_2), 3.33 (1H, dt, *J* = 6.9, 9.3 Hz, OCH<u>H</u>CH_2), 1.53-1.60 (2H, m, Alkyl-H), 1.23-1.33 (29H, m, Alkyl-H), 0.86-8.91 (3H, m, Alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.3 (C), 130.3 (CH), 130.2 (CH), 129.7 (C), 127.7 (CH), 114.1 (CH), 77.4 (CH), 68.6 (CH_2), 55.4 (CH_3), 32.1 (CH_2), 30.2 (CH_2), 29.9 (3 x CH_2), 29.8 (3 x CH_2), 29.78 (2 x CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.4 (CH_2), 22.9 (CH_2), 22.0 (CH_3), 14.3 (CH_3); Found (*p* APCI) $[M]^+$ 402.3490, $C_{27}H_{46}O_2$ requires 402.3492.

(*E*)-*S*-(4-(4-Methoxyphenyl)but-3-en-2-yl)benzothioate (147c)



Gold(I) catalysis:

Allylic alcohol **146** (12.5 mg, 0.070 mmol, 1.0 equiv.), thioacid **35o** (9.1 µl, 0.077 mmol, 1.1 equiv.) and Au(I)-catalyst **22** (2.3 mg, 5 mol%) and $CDCl_3$ (0.7 ml) were added to a vial and stirred at 30 °C for 60 mins. The crude mixture was purified by column chromatography (5:1 hexane/ether) to yield product **147c** as a colourless oil (78%, 16.3 mg, 0.055 mmol).

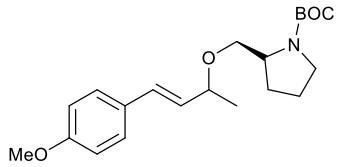
$InCl_3$ Catalysis:

A solution of allylic alcohol **146** (12.3 mg, 0.069 mmol, 1 equiv.) in $CDCl_3$ (0.15 ml) was added to a solution of $InCl_3$ (0.9 mg, 5 mol%) and thioacid **35o** (9.1 µl, 0.077 mmol, 1.1 equiv.) in $CDCl_3$ (0.35 ml). The vial containing the allylic alcohol solution was then rinsed with $CDCl_3$ (0.20 ml) and washings added to reaction mixture. The resulting mixture was stirred at 30 °C for 60 mins and then purified by column chromatography (3:1 hexane/ether) to yield product **147c** as a colourless oil (85%, 17.5 mg, 0.059 mmol). *Note: NMR of crude shows a mixture of formal S_N2' and S_N2 products but fully isomerises to the formal S_N2' product upon purification. Note: If reaction carried out in microwave (CEM Discover, sealed tube) at 0.1 M concentration, 99% yield is obtained.*

R_f 0.51 (3:1 hexane/ether); IR ν (cm^{-1}) 2962, 2930, 2834 (C-H), 1656 (C=O), 1606, 1579, 1510 (C-C Ar), 1246 (C-O-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.97 (2H, m, Ar-H), 7.53-7.59 (1H, m, Ar-H), 7.41-7.46 (2H, m, Ar-H), 7.32 (2H, d, *J* = 9.2 Hz, Ar-H), 6.84

(2H, d, *J* = 8.8 Hz, Ar-H), 6.62 (1H, d, *J* = 15.8 Hz, ArC<u>H</u>=CH), 6.18 (1H, dd, *J* = 7.6, 15.8 Hz, ArCH=C<u>H</u>) 4.50-4.65 (1H, m, =CHC<u>H</u>CH$_3$), 3.80 (3H, s, OCH$_3$), 1.60 (3H, d, *J* = 7.0 Hz, CHC<u>H$_3$</u>); ^{13}C NMR (100.6 MHz, CDCl$_3$) δ 191.5 (C), 159.4 (C), 137.4 (C), 133.4 (CH), 130.2 (CH), 129.6 (C), 128.7 (CH), 128.1 (CH), 127.8 (CH), 127.4 (CH), 114.1 (CH), 55.4 (CH$_3$), 41.4 (CH), 20.7 (CH$_3$); Found (*p* NSI) $[M + H]^+$ 299.1103, $C_{18}H_{19}O_2S$ requires 299.1100.

(2*R*)-1-(1-*tert*-Butoxy)vinyl)-2-((((*E*)-4-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)pyrrolidine (147d)



Gold(I) catalysis:

Allylic alcohol **146** (12.8 mg, 0.072 mmol, 1.0 equiv.), alcohol **127d** (71.1 mg, 0.35 mmol, 5.0 equiv.) and PPh$_3$AuNTf$_2$ (2:1 toluene adduct) (2.4 mg, 5 mol%) and CDCl$_3$ (0.7 ml) were added to a vial and stirred at 30 °C for 30 mins. The crude mixture was purified by column chromatography (7:1 to 5:1 to 3:1 hexane/ethyl acetate) to yield product **147d** as colourless oil (53%, 13.7 mg, 0.038 mmol).

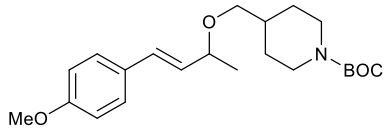
InCl$_3$ Catalysis:

A solution of allylic alcohol **146** (12.4 mg, 0.070 mmol, 1 equiv.) in CDCl$_3$ (0.15 ml) was added to a solution of InCl$_3$ (0.8 mg, 5 mol%) and alcohol **127d** (70.0 mg, 0.35 mmol, 5.0 equiv.) in CDCl$_3$ (0.35 ml). The vial containing the allylic alcohol solution was then rinsed with CDCl$_3$ (0.20 ml) and washings added to reaction mixture. The resulting mixture was stirred at 30 °C for 30 mins and then purified by column chromatography (7:1 to 5:1 to 3:1 hexane/ethyl acetate) to yield product **147d** as a colourless oil (90%, 22.7 mg, 0.063 mmol).

R_f 0.39 (3:1 hexane/ethyl acetate); IR ν (cm^{-1}) 2972, 2872 (C-H), 1690 (C=O), 1607, 1577, 1511 (C-C Ar), 1249 (C-O-C); ^{1}H NMR (300 MHz, CDCl$_3$, 55 ^{o}C) δ 7.30 (2H, d, *J* = 8.8 Hz, Ar-H), 6.85 (2H, d, *J* = 8.8 Hz, Ar-H), 6.46 (1H, d, *J* = 16.1 Hz, ArCH=C), 6.96 (1H, dt, *J* =16.1, 7.4 Hz, ArCH=CH), 4.02-3.83 (2H, m, OCH + OCHH), 3.81 (3H, s, OCH$_3$), 3.64-3.28 (4H, m, NCH$_2$, NCH + OCHH), 2.03-1.72 (4H, m, 2xCH$_2$), 1.45-

1.43 (9H, 2 x s, $C(CH_3)_3$ rotamers 1 & 2), 1.31-1.29 (3H, 2 overlapping d, $OCHCH_3$ rotamers 1 & 2); ^{13}C NMR (175 MHz, $CDCl_3$, 55 ^oC) δ 159.6 (C), 154.8 (C), 130.4 (C), 130.3 (CH), 130.2 (CH rotamer 1), 130.0 (CH rotamer 2), 127.8 (CH), 114.3 (CH), 79.2 (CH), 77.3 (C rotamer 1), 78.0 (C rotamer 2), 69.19 (CH_2), 69.17 (CH_2), 57.2 (CH, rotamer 1), 57.1 (CH, rotamer 2), 55.5 (CH_3), 46.9 (CH_2), 46.9 (CH_2), 28.8 (CH_3), 21.8 (CH_3, rotamer 1), 21.7 (CH_3, rotamer 2); Found (*p* NSI) $[M + Na]^+$ 384.2148, $C_{21}H_{31}NO_4Na$ requires 384.2145.

(*E*)-1-(1-*tert*-Butoxy)vinyl)-2-(((4-(4-methoxyphenyl)but-3-en-2-yl)oxy)methyl)piperidine (148e)



Gold(I) catalysis:

Allylic alcohol **146** (12.6 mg, 0.071 mmol, 1.0 equiv.), alcohol **127e** (74.0 mg, 0.35 mmol, 5.0 equiv.) and PPh_3AuNTf_2 (2:1 toluene adduct) (2.4 mg, 5 mol%) and $CDCl_3$ (0.7 ml) were added to a vial and stirred at 30 °C for 30 mins. The crude mixture was purified by column chromatography (7:1 to 5:1 to 3:1 hexane/ethyl acetate) to yield product **147e** as a colourless oil (71%, 19.0 mg, 0.051 mmol).

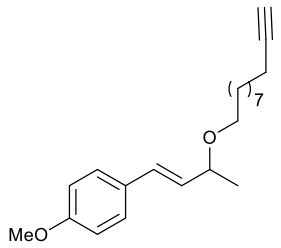
$InCl_3$ Catalysis:

A solution of allylic alcohol **146** (12.6 mg, 0.071 mmol, 1 equiv.) in $CDCl_3$ (0.15 ml) was added to a solution of $InCl_3$ (1.0 mg, 5 mol%) and alcohol **127e** (74.3 mg, 0.35 mmol, 5.0 equiv.) in $CDCl_3$ (0.35 ml). The vial containing the allylic alcohol solution was then rinsed with $CDCl_3$ (0.20 ml) and washings added to reaction mixture. The resulting mixture was stirred at 30 °C for 30 mins and then purified by column chromatography (7:1 to 5:1 to 3:1 hexane/ethyl acetate) to yield product **147e** as a colourless oil (72%, 19.2 mg, 0.051 mmol).

R_f 0.40 (3:1 hexane/ethyl acetate); IR ν (cm^{-1}) 2973, 2928, 2853 (C-H), 1688 (C=O), 1607, 1577, 1511 (C-C Ar), 1249 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.8 Hz, Ar-H), 6.86 (2H, d, *J* = 8.8 Hz, Ar_H), 6.44 (1H, d, *J* = 15.9 Hz, PhC<u>H</u>=CH), 5.94 (1H, dd, *J* = 7.6, 15.9 Hz, ArCH=C<u>H</u>), 4.01-4.16 (2H, m, C<u>H</u>HN), 3.92 (1H, qn, *J* = 6.6 Hz, $CH_3C\underline{H}O$), 3.81 (3H, s, OCH_3), 3.34 (1H, dd, *J* = 6.3, 9.2 Hz, OC<u>H</u>H), 3.17 (1H,

dd, *J* = 6.3, 9.2 Hz, OCHH), 2.69 (2H, app. br t, *J* = 12.3 Hz, CHHN), 1.66-1.78 (3H, m, alkyl-H), 1.45 (9H, s, *t*-butyl), 1.30 (3H, d, *J* = 6.6 Hz, CH_3CH), 1.05-1.15 (2H, m, alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.4 (C), 155.0 (C), 130.5 (CH), 129.9 (CH), 129.6 (C), 127.7 (CH), 114.1 (CH), 79.3 (C), 77.1 (CH), 73.2 (CH_2), 55.4 (CH_3), 44.0 (CH_2), 36.9 (CH), 29.4 (CH_2), 28.6 (CH_3), 21.8 (CH_3); Found (*p* NSI) $[M + Na]^+$ 398.2301, $C_{22}H_{33}NO_4Na$ requires 398.2302.

(*E*)-1-Methoxy-4-(3-(undec-10-yn-1-yloxy)but-1-ene-1-yl)benzene (147f)



Gold(I) catalysis:

Allylic alcohol **146** (12.3 mg, 0.069 mmol, 1.0 equiv.), alcohol **127j** (65 μl, 0.35 mmol, 5.0 equiv.) and PPh_3AuNTf_2 (2:1 toluene adduct) (2.4 mg, 5 mol%) and $CDCl_3$ (0.7 ml) were added to a vial and stirred at 30 °C for 30 mins. A complex mixture of products was obtained.

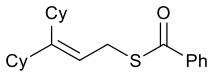
$InCl_3$ Catalysis:

A solution of allylic alcohol **146** (12.4 mg, 0.070 mmol, 1 equiv.) in $CDCl_3$ (0.15 ml) was added to a solution of $InCl_3$ (1.0 mg, 5 mol%) and alcohol **127j** (65 μl, 0.35 mmol, 5.0 equiv.) in $CDCl_3$ (0.35 ml). The vial containing the allylic alcohol solution was then rinsed with $CDCl_3$ (0.20 ml) and washings added to reaction mixture. The resulting mixture was stirred at 30 °C for 30 mins and then purified by column chromatography (7:1 hexane/ethyl acetate) to yield product **147f** as a colourless oil (79%, 18.2 mg, 0.055 mmol).

R_f 0.48 (5:1 hexane/ethyl acetate); IR ν (cm^{-1}) 3300 (C≡C-H) 2973, 2928, 2854 (C-H), 2117 (C≡C), 1607, 1577, 1511 (C-C Ar), 1249 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32 (2H, d, *J* = 8.7 Hz, Ar-H), 6.85 (2H, d, *J* = 8.7 Hz, Ar-H), 6.45 (1H, d, *J* = 15.9 Hz, ArCH=CH), 5.98 (1H, dd, *J* = 7.6, 15.9 Hz, ArCH=CH), 3.95 (1H, qn, *J* = 6.5 Hz, $CHCHCH_3$), 3.81 (3H, s, OCH_3), 3.48 (1H, dt, *J* = 6.8, 9.3 Hz, OCH_2CH_2), 3.30 (1H, dt, *J* = 6.8, 9.3 Hz, OCH_2CH_2), 2.17 (2H, td, *J* = 2.7, 7.1 Hz, $CH_2C{\equiv}CH$), 1.93 (1H, t, *J* = 2.7

Hz, C≡C<u>H</u>), 1.45-1.63 (5H, m, alkyl-H), 1.23-1.43 (12H, m, alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.3 (C), 130.4 (CH), 130.2 (CH), 129.7 (C), 127.7 (CH), 114.1 (CH), 84.9 (C), 77.4 (CH), 68.5 (CH), 68.2 (CH), 55.4 (CH_3), 30.1 (CH_2), 29.6 (2 x CH_2), 29.2 (CH_2), 28.9 (CH_2), 28.6 (CH_2), 26.4 (CH_2), 21.9 (CH_3), 18.5 (CH_2); Found (*p* APCI) $[M-H]^+$ 327.2317, $C_{22}H_{31}O_2$ requires 327.2319.

_S_-(4,4-Dicyclohexylbut-3-en-2-yl)benzothioate (150)



Gold(I) catalysis:

Scale up from 0.07-1.0 mmol

A solution of allylic alcohol **149** (223.6 mg, 1.00 mmol, 1.0 equiv.) in $CHCl_3$ (1.0 ml) was added to a vial containing thioacid **35o** (130 μL, 1.1 mmol, 1.1 equiv.), Au(I)-catalyst **6** (38.3 mg, 5 mol%), and $CHCl_3$ (8 ml). Vial washed with $CHCl_3$ (1.0 mL) and added to mixture. The resulting reaction mixture was stirred at 50 °C for 2 hours and then concentrated. The crude mixture was purified by column chromatography (7:1 hexane/ether) to yield product **150** as a colourless oil (82%, 280.2 mg, 0.819 mmol).

$InCl_3$ Catalysis:

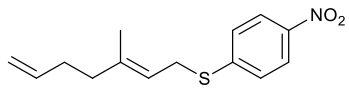
Scale up from 0.07 – 1.0 mmol

A solution of allylic alcohol **149** (221.1 mg, 1.0 mmol, 1 equiv.) in $CHCl_3$ (1.0 ml) was added to a vial containing $InCl_3$ (10 mg, 5 mol%), thioacid **35o** (130 μl, 1.1 mmol, 1.1 equiv.) and $CHCl_3$ (8 ml). The vial was washed with $CHCl_3$ (1.0 ml) and added to reaction mixture. The resulting reaction mixture was stirred at 50 °C for 2 hours and then purified by column chromatography (7:1 hexane/ether) to yield product **150** as a colourless oil (97%, 331.5 mg, 0.969 mmol).

R_f 0.76 (3:1 hexane/ether); IR ν (cm^{-1}) 2922, 2849 (C-H), 1660 (C=O), 1596, 1581, 1447 (C-C Ar); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95-7.98 (2H, m, Ar-H), 7.53-7.58 (1H, m, Ar-H), 7.41-7.46 (2H, m, Ar-H), 5.27 (1H, t, *J* = 8.1 Hz, C=C<u>H</u>CH_2), 3.81 (2H, d, *J* = 8.1 Hz, C=CHC<u>H_2</u>), 2.45-2.54 (1H, m, Alkyl-H), 1.87-1.85 (1H, m, Alkyl-H), 1.50-1.80 (10H, m, Alkyl-H), 1.08-1.40 (10H, m, Alkyl-H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 192.5 (C), 155.7 (C), 137.4 (C), 133.3 (CH), 128.7 (CH), 127.3 (CH), 116.0 (CH), 41.1 (CH),

40.7 (CH), 34.9 (CH_2), 31.1 (CH_2), 27.2 (CH_2), 27.1 (CH_2), 26.7 (CH_2), 26.4 (CH_2), 26.3 (CH_2); Found (*p* APCI) $[M + H]^+$ 343.2087, $C_{22}H_{31}OS$ requires 343.2090

(*E*)-(3-Methylhepta-2,6-dien-1-yl)(4-nitrophenyl)sulfane (154)



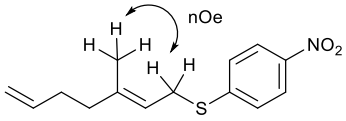
Gold(I) catalysis:

Allylic alcohol **153** (8.7 mg, 0.070 mmol, 1.0 equiv.), thiol **35b** (11.8 mg, 0.079 mmol, 1.1 equiv.) and Au(I) catalyst **22** (2.9 mg, 5 mol%) and $CDCl_3$ (0.7 ml) were added to a sealed tube and the resulting mixture stirred at 80 °C for 30 mins. The crude mixture was purified by preparative thin layer chromatography (20:1 hexane/ethyl acetate) where to yield the product **154** as yellow oil (15%, 2.7 mg, 0.010 mmol).

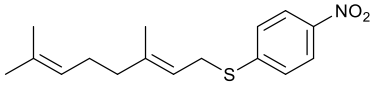
$InCl_3$ Catalysis:

A solution of allylic alcohol **153** (8.5 mg, 0.067 mmol, 1 equiv.) in $CDCl_3$ (0.15 ml) was added to a solution of $InCl_3$ (0.8 mg, 5 mol%) and thiol **35b** (11.3 mg, 0.075 mmol, 1.1 equiv.) in $CDCl_3$ (0.35 mL). The vial containing the allylic alcohol solution was then rinsed with $CDCl_3$ (0.20 ml) and washings added to the reaction mixture. The resulting reaction mixture was stirred at 80 °C for 30 mins and then purified by column chromatography (7:1 hexane/ethyl acetate) to yield the product **154** as a yellow oil (48%, 8.4 mg, 0.032 mmol).

R_f 0.56 (5:1 hexane/ethyl acetate); IR ν (cm^{-1}) 2923 (C-H), 1640 (C=C), 1593, 1577, 1478 (C-C Ar), 1510 1335 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) *E*/*Z* 3:1 δ 8.11 (2H + 2H', d, *J* = 9.1 Hz, Ar-H), 7.32 (2H + 2H', d, *J* = 9.1 Hz, Ar-H), 5.67 -5.88 (1H + 1H', m, alkene CH) 5.28-5.37 (1H + 1H', m, alkene CH), 4.91-5.07 (2H + 2H', m, C$\underline{H}_2$=CH), 3.67 (2H + 2H', d, *J* = 7.5 Hz, C$\underline{H}_2$S), 2.08-2.22 (4H + 4H', m, C$\underline{H}_2$C$\underline{H}_2$), 1.76 (3H', app. d, *J* = 1.2 Hz, CH_3, *Z* isomer, minor), 1.73 (3H, app. d, *J* = 0.5 Hz, CH_3, *E* isomer, major);^{13}C NMR (300 MHz, $CDCl_3$) δ 148.2 (C, major + minor), 145.1 (C, major + minor), 141.2 (C, major + minor), 138.03 (CH, major), 137.98 (CH, minor), 126.6 (CH, major), 126.5 (CH, minor), 124.0 (CH, minor), 123.97 (CH, major), 118.4 (CH_2, minor), 118.1 (CH_2, major), 115.3 (CH, minor), 115.0 (CH, major), 38.9 (CH_2, major + minor), 32.2 (CH_2, minor), 32.0 (CH_2, major), 30.55 (CH_2, major), 30.48 (CH_2, minor), 16.5 (CH_3, major + minor); Found (*p* APCI) $[M + H]^+$ 264.1050, $C_{14}H_{18}NO_2S$ requires 264.1053.



(E)-(3,7-Dimethylocta-2,6-dien-1-yl)(4-nitrophenyl)sulfane (155)



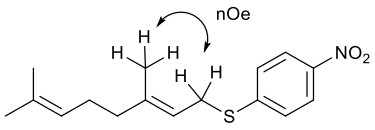
Gold(I) catalysis:

Linalool **130** (10.6 mg, 0.069 mmol, 1.0 equiv.), thiol **35b** (11.4 mg, 0.076 mmol, 1.1 equiv.) and Au(I) catalyst **6** (3.0 mg, 5 mol%) and $CDCl_3$ (0.7 ml) were added to a vial and the resulting mixture stirred at 50 °C for 4 hours. The crude mixture was purified by preparative thin layer chromatography (20:1 hexane/ethyl acetate) where to yield the product **155** as a yellow oil (16%, 3.3 mg, 0.011 mmol).

$InCl_3$ Catalysis:

A solution of linalool **130** (11.0 mg, 0.071 mmol, 1 equiv.) in $CDCl_3$ (0.15 ml) was added to a solution of $InCl_3$ (0.9 mg, 5 mol%) and thiol **35b** (11.2 mg, 0.075 mmol, 1.1 equiv.) in $CDCl_3$ (0.35 mL). The vial containing the linalool solution was then rinsed with $CDCl_3$ (0.20 ml) and washings added to the reaction mixture. The resulting reaction mixture was stirred at 50 °C for 4 hours and then purified by preparative thin layer chromatography (20:1 hexane/ethyl acetate) to yield the product **155** as a yellow oil (31%, 6.4 mg, 0.022 mmol). *Note: Product **155** (28%, 5.8 mg, 0.02 mmol) can also be synthesised via this method using geraniol **156** as the allylic alcohol instead of linalool **130**.*

R_f 0.36 (20:1 hexane/ethyl acetate); IR ν (cm^{-1}) 2922 (C-H), 1593, 1577, 1478 (C-C Ar), 1511 1335 (NO_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (2H, d, *J* = 9.1 Hz, Ar-H), 7.32 (2H, d, *J* = 9.1 Hz, Ar-H), 5.30 (1H, tq, *J* = 1.2, 6.3 Hz $(CH_3)_2C{=}CC\underline{H}$), 5.00-5.07 (1H, m, $=C\underline{H}CH_2S$), 3.67 (2H, d, *J* = 7.5 Hz, $=CHC\underline{H_2}S$), 2.02-2.14 (4H, m, $CHC\underline{H_2}C\underline{H_2}$), 1.58-1.77 (9H, m, $C\underline{H_3}$);^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.3 (C), 141.8 (C), 132.1 (C), 126.6 (CH), 125.7 (C), 124.0 (CH), 123.7 (CH), 117.7 (CH), 39.6 (CH_2), 30.6 (CH_2), 26.4 (CH_2), 25.8 (CH_3), 17.9 (CH_3), 16.5 (CH_3); Found (*p* APCI) $[M + H]^+$ 292.1366, $C_{16}H_{22}NO_2S$ requires 292.1366.


nOe
H
H
H
H
S
NO2

3.6 References

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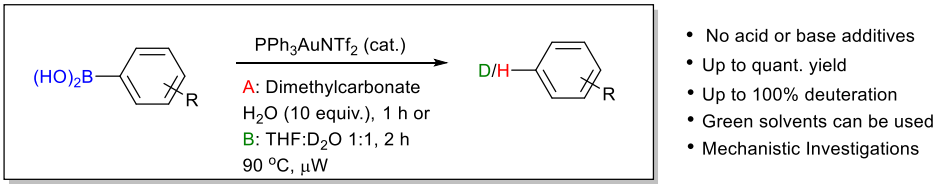
Chapter 4: A Mild Catalysed Proto- and Deuterodeboronation using Gold Catalysis



Acknowledgements

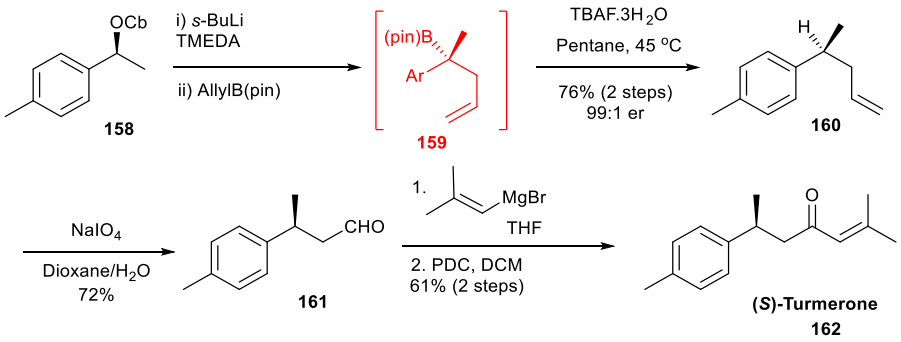
The author would like to thank the following people who collaborated on this project: Graeme Barker, David Johnson, Matthew Andrews, Rachel Curley and Paul Young. Where work has been carried out by anyone other than the author, this has been explicitly stated.

4.1 Introduction

4.1.1 Protodeboronation

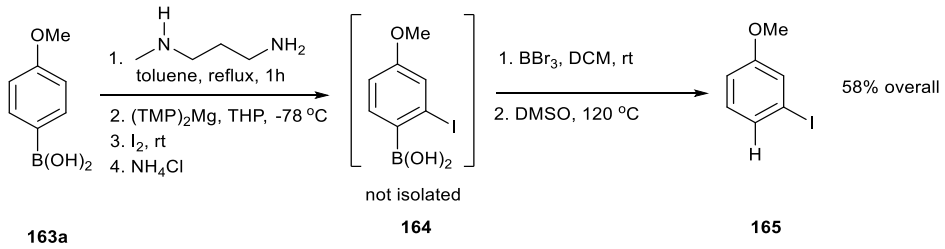
Aryl boronic acids are widely available and readily used in organic chemistry.[1] For example, boronic acids are widely utilised in Pd-catalysed coupling reactions, such as the Suzuki-Miyaura reaction, where organoboron compounds are much cheaper than their tin counterparts, tolerate a wide range of functional groups and produce by-products which are not as harmful to the environment.[2] In these reactions protodeboronation is usually considered an unwanted side reaction. In fact, certain boronic acids, usually heterocyclic boronic acids, are prone to deprotonation on storage.[3]

However, recently many groups have taken advantage of protodeboronation and have applied this step in organic synthesis. In 2010, Aggarwal and co-workers utilized the protodeboronation of alkyl boronic esters to perform an asymmetric synthesis of tertiary alkyl stereogenic centres with yields >79% and excellent retention of stereochemistry. Subsequent to this they were able to utilise the protodeboronation step (highlighted in red, Scheme 4.1) to synthesise (*S*)-Turmerone **162**.[4] This reaction was further developed by Aggarwal and co-workers to include the synthesis of highly enantioenriched tertiary alcohols[5] as well as enantioenriched *gem*-diarylalkyl compounds, the latter being present in many therapeutically important molecules.[6]



Scheme 4.1: Total synthesis of (*S*)-Turmerone ultilsing protodeboronation.

Cheon and co-workers and have also exploited the protodeboronation reaction, whereby the boronic acid was used as a traceless blocking or directing group on aryls (Scheme 4.2). They then performed a protodeboronation reaction allowing access to a *meta*-directed substituent with electron donating groups.[7]

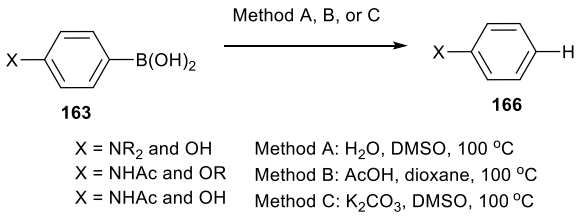


163a **164** **165**

Scheme 4.2: Use of boronic acid as a traceless directing group for the synthesis of *meta*-iodophenol

However, protodeboronation reactions are usually subject to harsh conditions, such as strong acids or bases and are highly substituent dependant. For example Kuivila *et al.* found that the rate of protodeboronation of 2,6-dimethoxybenzeneboronic acid was greatly enhanced when the pH of the reaction was decreased, suggesting acid catalysis. However, if electron withdrawing groups were present on the aryl boronic acid, protodeboronation did not occur.[8] In a complementary report 50 years later, Perrin and co-workers found that electron deficient 2,6-disubstituted aryl boronic acids require basic conditions in order to protodeboronate efficiently.[9]

These problems were again highlighted in Cheon's work as only boronic acids with an *ortho*- or *para*-OH group or very electron donating NR_2 groups (Scheme 4.3, Conditions A) were able to undergo protodeboronation in the absence of an acid or a base. However, moderately electron rich boronic acids (Scheme 4.3, Conditions B or C) require the use of an acid or a base, thus preventing the use of acid and base sensitive functional groups (Scheme 4.3).[7]



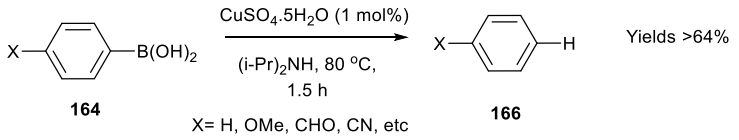
163 **166**

Scheme 4.3: Summary of Cheon's work on protodeboronation of aryl boronic acids

In recent years, transition metal-catalysed protodeboronation reactions have been studied. Transition metals used include Cu-[10], Ag,[11] and Pd,[12] but the drawback of these reactions is that they still require stoichiometric amounts of base in order for the protodeboronation to be successful.

The copper-catalysed protodeboronation reaction (without Cu catalyst a 54% yield was obtained) by Liu *et al.* was high yielding and had a wide substrate scope including

electron-rich and electron withdrawing groups as well as several heterocycles (Scheme 4.4). However, the substrate scope is once again limited by the need for a base, hence no base sensitive substrates could undergo protodeboronation *via* this method.[10]



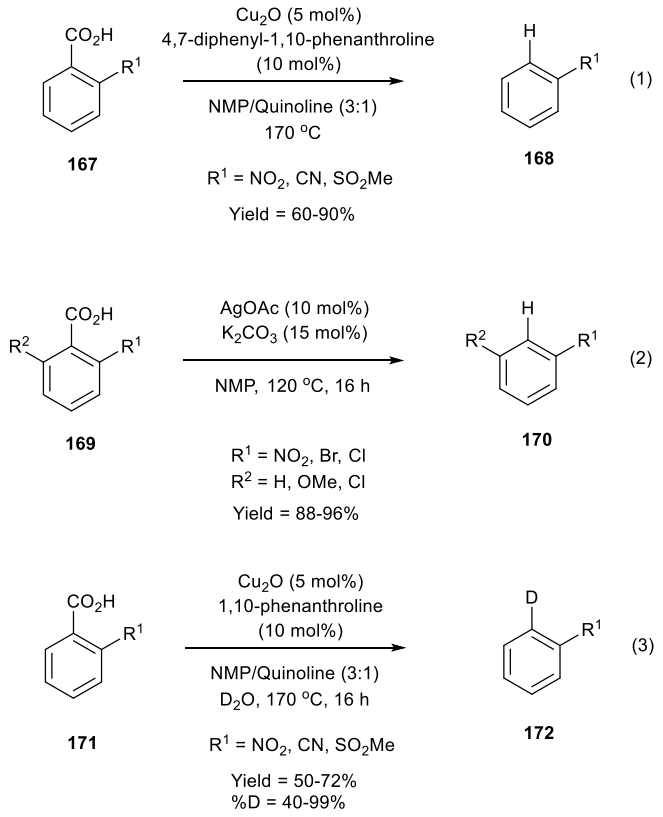
Scheme 4.4: Cu-catalysed protodeboronation of aryl boronic acids

To summarise, there have been several examples of protodeboronation reactions in recent years. However, these reactions usually involve an acid or a base and therefore base and acid sensitive functional groups are not tolerated. At the onset of this project, a mild and additive free procedure (no acids or bases) which tolerates a wide variety of functional groups was not available.

4.1.2 Deuterodeboronation

Protodeboronation of boronic acids could also be adapted for deuterodeboronation. A practical *ipso*-deuteration technique would be extremely useful in synthetic chemistry. The inclusion of deuterium atoms in organic molecules is highly desirable, as it has many wide ranging applications,[13] including mechanistic investigations,[14] isotopically labelled internal standards,[15] as well as in pharmokinetic and metabolic studies in drug development.[16] Deuterodeboronation is only mentioned briefly by Perrin and co-workers and is limited to one example.[9] However, there are numerous examples of the related proto- and deutero-decarboxylations at the *ipso* position of aromatic carboxylic acids which will be briefly reviewed here.

In 2011, Gooßen and co-workers developed a proto- and deutero-decarboxylation of aryl carboxylic acids by utilising Cu- and Ag- as catalysts.[17] For *meta*- and *para*- electron deficient benzoic acids, the copper based catalyst was found to give high yields of products (Scheme 4.5, Eq. 1). However, for *ortho*-substituted benzoic acids silver based catalysts were found to be more effective with the copper catalyst either being low yielding or no reaction taking place (Scheme 4.5, Eq. 2).[17]



Scheme 4.5: Proto- and deutero-decarboxylation by Gooßen and co-workers.

Having successfully carried out protodecarboxylation, the use of deuterons rather than protons were considered. From their optimisation, it was observed that the copper-based catalyst system was the most effective for the reaction, giving moderate to good yields (54-77%) with the % incorporation of deuterium atoms ranging from 40-99% (Scheme 4.5, Eq. 3). However, these procedures have their limitations. The reactions must be performed at high temperatures 120-170 °C, long reaction times are required (16 h) and the method only works for electron deficient benzoic acids.[17]

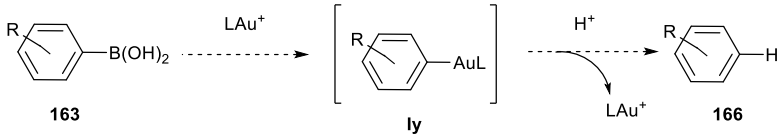
This reaction was then further developed by Larrosa and co-workers, but in this case only catalytic amounts of Ag(I) salts were used.[18] Although the % of deuterium incorporated into the products increases, 95-98%, the method suffers from limitations. Only electron-deficient benzoic acids or heterocycles are tolerated and again high temperatures and long reaction times are required (120 °C, 16 h).[18]

A similar reaction was also published by Greaney and co-workers where Ag(I) salts were found to be the most effective catalyst and again electron deficient benzoic acids proceeded to protodecarboxylate efficiently.[19]

It is clear deuterodecarboxylation reactions require harsh conditions and is only effective for electron deficient benzoic acids. Thus, a mild deuterodeboronation reaction, especially one that can overcome the shortcomings of the related deuterodecarboxylation, is highly desirable.

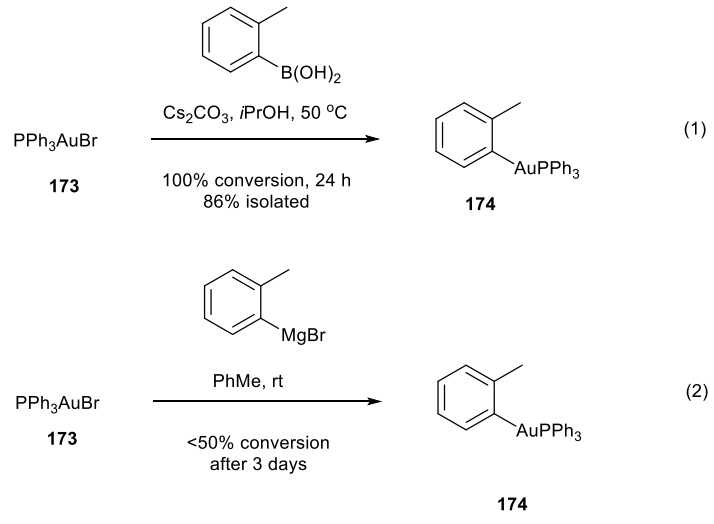
4.1.3 Transmetallation of gold species from boronic acids

The aim of the project was to develop a mild gold(I) catalysed protodeboronation reaction, presumably *via* organogold intermediate **Iy** (Scheme 4.6). The formation of **Iy** is in fact known in stoichiometric reactions.



Scheme 4.6: Aim: mild gold(I) catalysed protodeboronation reaction *via* organogold intermediate

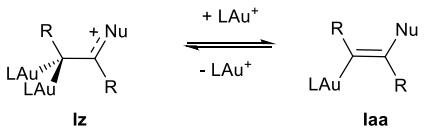
Gray and co-workers were able to isolate the mononuclear gold species **174** and form an aryl carbon gold bond by selective transmetallation of boronic acids in the presence of a base (Scheme 4.7, Eq. 1) in good yields after 24 hours at 50 °C. This method provides an improvement on other procedures which required a Grignard reagent (less than a 50% conversion after 3 days (Scheme 4.7, Eq. 2).[20]



Scheme 4.7: synthesis of monogold complex *via* boronic acids and Grignard reagents.

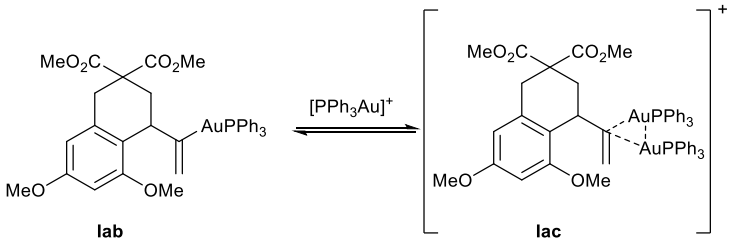
However, more interestingly, dinuclear gold species have also been isolated and are thought to represent the catalysts resting state.[21] Hoffman and co-workers first suggested the idea of a dinuclear species in 1982 whereby the isolobal relationship between a proton

and an LAu^+ fragment suggests that the catalyst could react with itself (Scheme 4.8, **Iaa**) competing with the protodeauration step to produce intermediate **Iz**, especially due to the carbophilic nature of gold.[22]



Scheme 4.8: Possible competing pathway to produce dinuclear species

This theory was then confirmed by Gagné and co-workers in 2009 where they described the synthesis and the characterisation by NMR of a diaurated species in the gold catalysed cyclisation of allenes (Scheme 4.9).[21]



Scheme 4.9: Gold-vinyl intermediates in the hydroarylation of allenes

Gagné then further developed this chemistry to include aryl complexes, where they were able to characterise the following digold species, **175** (Figure 4.1).

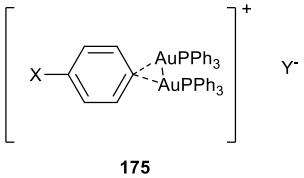
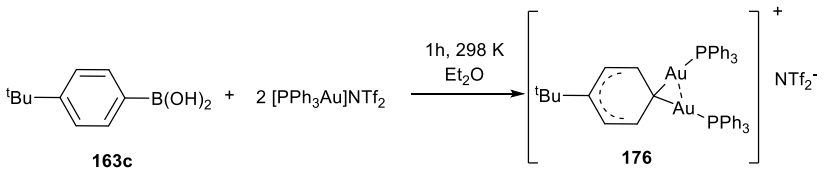


Figure 4.1: Digold aryl species – X = ED/EWG, Y=counterion

Gagné and co-workers determined that the formation of the digold species was dependant on the counterion used. It was observed that the digold species was only formed when less coordinating counterions (TFA, OTs, NTf_2) were used. When strongly coordinating ligands were used (OAc, OBz), the digold species was not observed. They noted that with electron withdrawing substituents, the digold species was only formed when the least coordinating anions where used.[23]

These species can also be observed by reacting two equivalents of PPh_3AuNTf_2 with aryl boronic acids.[24] This method is mild, quick and high yielding compared to the previous procedures which involved the use of silver salts, Bronsted acids or Grignard reagents.



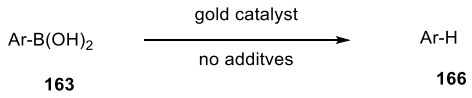
163c 176

Scheme 4.10: Stoichiometric reaction with aryl boronic acids and 2 PPh_3AuNTf_2 to form digold species

Gray and co-workers were able to isolate and determine the crystal structures *via* x-ray diffraction for several *gem*-diaurated species. Although these species were stable as solids at room temperature, they rapidly decomposed in solution. By applying this method, both electron rich, electron poor and heterocyclic boronic acids could be utilised to synthesise the diaurated species.[24] This work by Gray is of relevance as the formation of the dinuclear species **176** is presumably *via* the organogold species **Iy**, thereby providing evidence that organoboronic acids can transmetallate with PPh_3AuNTf_2 in the absence of an acid or a base to form **Iy** (Scheme 4.6).

4.2 Project Aims

At the outset of this project the Lee group aimed to develop a mild, gold catalysed, additive free (i.e. no acids or bases) protodeboronation reaction, whereby, aryl or heterocyclic boronic acids containing either acid or base sensitive functional groups (not tolerated under previous conditions) with both electron rich and electron poor aryl boronic acids would undergo protodeboronation.

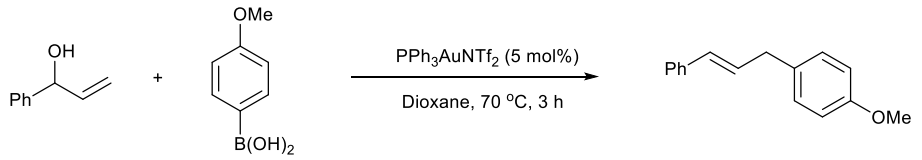


Scheme 4.11: Project aim – protodeboronation of boronic acids under mild conditions without additives

Should this reaction be successful, the group would then aim to utilise this chemistry to explore deuterodeboronations.

4.3. Previous Work

Recent interests within the Lee group involve investigations into gold-catalysed reactions with allylic alcohols and cyclopropenes with various nucleophiles including alcohols, thiols and indoles.[25] To further expand the nucleophile scope, the use of aryl boronic acids was investigated.[a] The preliminary results (Scheme 4.12) with allylic alcohol **177** and arylboronic acid **163a** produced the desired product **178** under gold catalysis. However, it soon became apparent after further investigations that the reaction was only ever successful with arylboronic acid **163a**.



177 **163a** **178**

Scheme 4.12: Initial investigations using arylboronic acids as nucleophiles

After further control experiments it was deduced that the reaction shown in Scheme 4.12 involves gold-catalysed protodeboronation of the arylboronic acid **163a**, followed by a Friedel-Crafts type allylation[26] of the resulting aryl to form the desired product **178**. However, other boronic acids were less successful due to the self-reaction between the allylic alcohol when protodeboronation does not occur efficiently. Due to the success of the protodeboronation step observed in this reaction and the increasing interest in protodeboronation as a tool in synthesis, the Lee group proceeded to optimise the reaction.

Initial optimisation studies carried out by Rachel Curley (MChem Student) is shown. The solvent screen was carried out using arylboronic acid **163d** and PPh_3AuNTf_2 (developed by Gagsoz)[27] as the catalyst (Table 4.1).

[a] Carried out by Paul C. Young, Heriot-Watt University

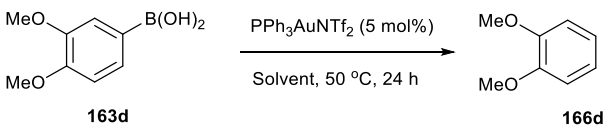


Table 4.1: Solvent Screen

Entry	Solvent	Yield (%)[a]
1	Chloroform	54
2	Acetonitrile	20
3	Toluene	24
4	Acetone	49
5[b]	Water	8
6	Dioxane	84
7	THF	97
8	2-Methyl THF	Quantitative
9	Dimethylcarbonate	Quantitative

[a]Determined using ^{1}H NMR analysis of the crude reaction using dimethylsulfone as an internal standard. [b]Poor solubility.

It was observed that both 2-methyl THF and dimethylcarbonate were excellent solvents for this reaction (Table 4.1, entries 8 and 9). Upon consulting the solvent selection guide by GSK, it was decided that dimethyl carbonate would be used for subsequent reactions due to its green credentials.[28] Next, the effects of catalyst loading and temperatures were investigated (Table 4.2).

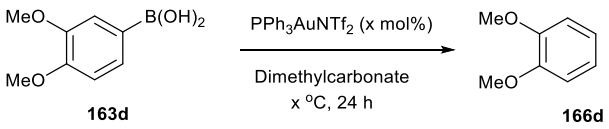


Table 4.2: Catalyst loading and temperature screen

Entry	Temp (°C)	Mol% Cat.	Yield (%)[a]
1	50	1	16
2	50	3	62
3	30	5	34
4	40	5	47
5	50	5	Quant.

[a]Determined using ^{1}H NMR analysis of crude reaction mixture using dimethylsulfone as an internal standard.

From these investigations it was deduced that lowering the temperature from 50 °C is detrimental to the reaction and produces lower yielding reactions with incomplete conversions (entries 3-5). This was also true in the case of lowering the catalyst loading (entries 1-3). Therefore, our optimised conditions were 50 °C, 5 mol% PPh_3AuNTf_2 for 24 hours. However, at the beginning of our substrate scope[b] it soon became apparent that this particular set of conditions only applied to electron-rich boronic acids (Table 4.3) and that increasingly harsh conditions were required for electron-withdrawing boronic acids; increasing the catalyst loading to 10 mol% or time to 48 hours produced only a 57% yield (entry 3).

[b] Carried out by Rachel Curley (MChem Student)

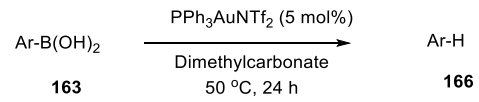


Table 4.3: Initial screening of electron-rich and electron-poor boronic acids

Entry	Aryl	Yield[a]
1	*m,p*-$OMeC_6H_3$ **163d**	Quant.
2	*p*-OHC_6H_4 **163e**	Quant.
3	*p*-$CO_2EtC_6H_4$ **163f**	48
4	*m*-$CO_2MeC_6H_4$ **163g**	41

[a]Determined using ^1H NMR analysis of the crude reaction mixture using dimethylsulfone as an internal standard.

However, by increasing the temperature to 70-90 °C and by using microwave heating this problem was overcome, and reaction times were dramatically reduced. A wide variety of substrates underwent the protodeboronation reaction under Au(I) catalysis, including electron-rich, electron-poor, sterically hindered, base- and acid sensitive boronic acids (section 4.4.1, Table 4.5).

Next, other aryl boronic acid derivatives, including arylboroxines **179**, aryl boronic esters **180**, aryltrifluoroborate **181** and MIDA boronate **182** were investigated (Table 4.4).[c]

[c] Carried out by Dr. Graeme Barker (Heriot-Watt University) and Matthew Andrews (Summer Student)

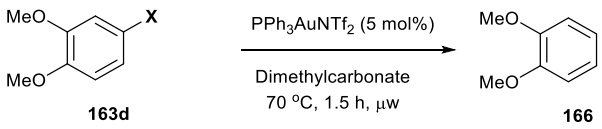
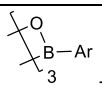
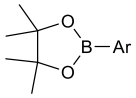
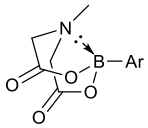


Table 4.4: Investigation of other arylboronic acid derivatives

Entry	X	Yield (%)[a]
1[b]	$(HO)_2B—Ar$ **163**	Quant.
2[c]	 **179**	No Conv.
3[d]	 + H_2O **179**	Quant.
4	 **180**	No conv.
5	$KF_3B—Ar$ **181**	No conv.
6	 **182**	No conv.

[a]Determined using ^1H NMR analysis of crude reaction mixture using dimethylsulfone as internal standard. [b]Arylboronic acid freshly recrystallized from water. [c]Arylboroxine from dehydrating arylboronic acid **x** *via* heating under vacuum. [d]10 equiv. of H_2O added to reaction mixture.

It was established that derivatives of arylboronic acids do not undergo the protodeboronation reaction under these conditions (entries 2, 4-6). However, since the arylboroxine **179** is readily formed by dehydrating the arylboronic acid **163**, it was deemed practical to add 10 equivalents of water to the reaction mixture to allow quantitative protodeboronation. Commercially available boronic acids usually contain a mixture of boronic acid and the boroxine and the ratio depends on the boronic acid used, with electron-rich boronic acids more stable in their boroxine form compared to electron-deficient boronic acids.[29] Thus, 10 equivalents of water was added to the reaction mixture

to ensure complete protodeboronation by *in situ* hydrolysis of the boroxine to the boronic acid.

4.4 Results and Discussion

4.4.1 Protodeboronation

Once the reaction conditions were optimised an aryl boronic acid scope was carried out (Table 4.5).

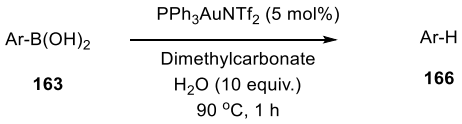
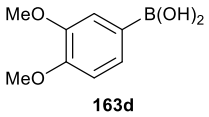
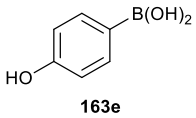
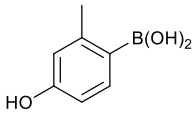
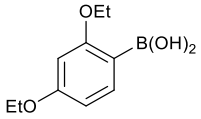
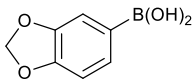
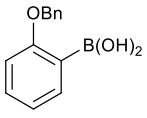
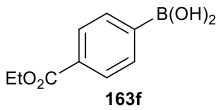
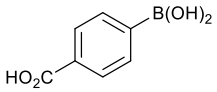
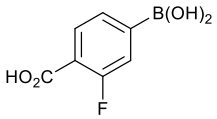
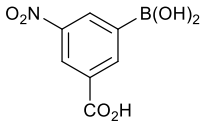
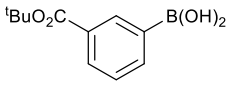
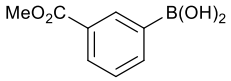
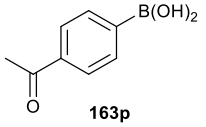
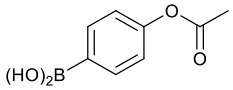
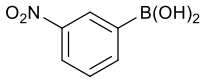
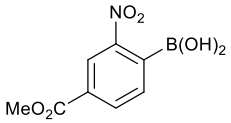
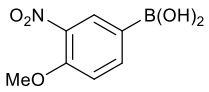
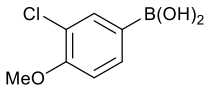
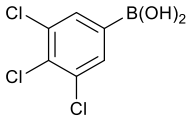
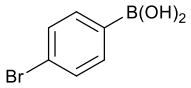
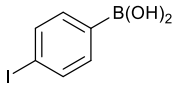
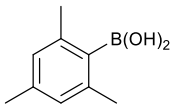
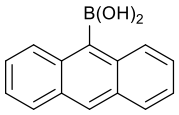
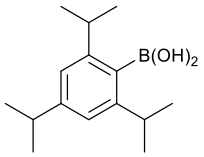
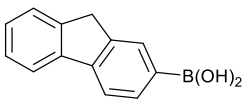
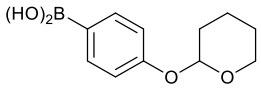
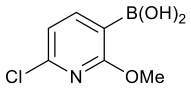
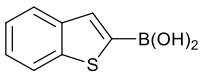
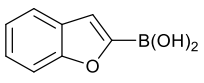
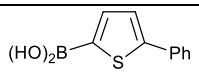
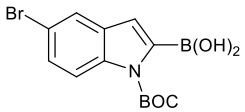
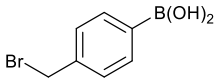
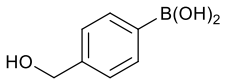
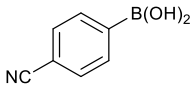


Table 4.5: Aryl boronic acid scope

Entry	Arylboronic acid	Product	Yield (%)[b]
1*[c]	 **163d**	**166d**	90
2**	 **163e**	**166e**	65[d]
3***	 **163h**	**166h**	92
4***	 **163i**	**166i**	90
5	 **163j**	**166j**	62[d]
6	 **163k**	**166k**	93
7*	 **163f**	**166f**	84

8	 **163l**	-	No conv.
9	 **163m**	-	No conv.
10	 **163n**	-	No conv.
11***	 **163o**	**166o**	92[e]
11a		**166o'**	30[f]
12***	 **163g**	**166g**	89
13[g]	 **163p**	**166p**	65
14	 **163q**	**166q**	37
15***	 **163r**	**166r**	92
16***	 **163s**	**166s**	70
17**	 **163t**	**166t**	97
18	 **163u**	**166u**	47[d]

19***	 **163v**	-	No conv.
20***	 **163w**	**166w**	47[d]
21***	 **163x**	-	No conv.
22	 **163y**	**166y**	95[d,h]
23**[i]	 **163z**	**166z**	99
24[j]	 **163aa**	**166aa**	99
25**	 **163ab**	**166ab**	74
26[f,k]	 **163ac**	**166ac**	83
27[j]	 **163ad**	**166ad**	72
28	 **163ae**	**166ae**	100
29	 **163af**	**166af**	33[l]

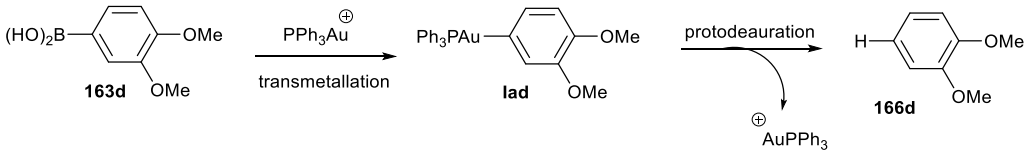
30	 163ag	**166ag**	85
31[f]	 163ah	**166ah**	73
32***	 163ai	-	No conv.
33***	 163aj	-	No conv.
34***	 163ak	-	No conv.

*Carried out by Rachel Curley. **Carried out by Matthew Andrews. ***Carried out by Graeme Barker. [a]Commercial aryl boronic acid. 10 equiv. H_2O added to ensure any arylboroxine is hydrated to the arylboronic acid, except entries 1,2,7 and 13. [b]isolated yields. [c]70 °C for 1.5 h. [d]Volatile product. [e]Carboxylic acid product. [f]Unactivated 4 Å MS added. [g]2 x 5 mol% Au(I) added over 4 h. [h]Reaction done in THF-d_8 and yield determined by ^{1}H NMR analysis using dimethylsulfone as internal standard. [i]2 hours. [j]3 hours. [k]4 hours. [l]Yield determined using ^{1}H NMR analysis of the crude using dimethylsulfone as an internal standard.

It can be seen from Table 4.5 that electron-rich boronic acids containing substituents in the *ortho*, *meta*, and *para* positions relative to the boronic acid (entries 1-6) efficiently protodeboronate to give excellent yields (>90%) with the exception of entries 2 and 5 which have only a moderate yield due to the volatile nature of the products. Electron-poor boronic acids again containing substituents in the *ortho*, *meta*, and *para* positions relative to the boronic acid again perform well (entries 7, 11-19), the exception being boronic acids which have a carboxylic acid moiety which appears to inhibit the reaction (entries 8-10). However, the carboxylic acid was easily obtained by protodeboronation and then saponification of the *tert*-butyl ester (Entry 11). Nevertheless, ester groups generally perform well (entries 7 and 12, 84 and 90% respectively) and the saponification step with the *tert*-butyl ester (entry 11a) can be partially stopped by adding unactivated molecular sieves to the reaction. However, the yield is still less than 50%. Unprotected base sensitive ketones (entry 13), as well as chloro- and bromo- substituted aryl boronic acids (entries 18-20) are tolerated, with the exception of the base sensitive acetate **163q**

(entry 14) which produced a 37% yield of the protodeboronated product as well as 22% yield of phenol. It should be noted that the addition of molecular sieves to this reaction did not improve the yield. Aryl iodides do not react under these conditions (entry 21). Sterically hindered boronic acids protodeboronate efficiently to yield products **163y-163aa** in yields upwards of 95% (entries 21-24). The acid sensitive THP acetal boronic acid **163ac** (entry 26) is also tolerated as long as unactivated molecular sieves are added to the reaction mixture (molecular sieves are thought be slightly basic and therefore, mop up any trace acid produced by the reaction which would deprotect the acetal).[30] This particular substrate required longer reaction times and it is thought that the addition of molecular sieves greatly reduced the speed of the reaction. Next, several heterocycles were investigated. In general, heterocycles performed well with yields ranging from 72-100% (entries 27, 28 and 30) with the exception of benzofuran **163af** which gave a poor yield of 33% (entry 29). A BOC- protected indole also worked well, 73% (entry 31) but again due to the acid sensitive nature of the protecting group molecular sieves were needed to give good selectivity for the BOC-protected indole **163ah**. However, entries 32-34 failed to react under these conditions even with the addition of molecular sieves to the reaction mixture. It is not understood why these particular boronic acids failed to react although inhibition of the gold catalyst by the functional groups is one probability.

4.4.2 Mechanistic and Computational Studies



Scheme 4.13: Initial proposed mechanism

The initial mechanism was originally thought to proceed by transmetallation of **163d** with Au(I) to form **Iad**, followed by protodeauration to release the catalyst and product **166d** (Scheme 4.13). However, our collaborators Dr. David Johnson and Prof. Stuart Macgregor carried out DFT calculations which suggest that the proposed intermediate is highly unlikely. Calculations suggest a mechanism where water plays a significant role in the trasmetallation step (Figure 4.2).

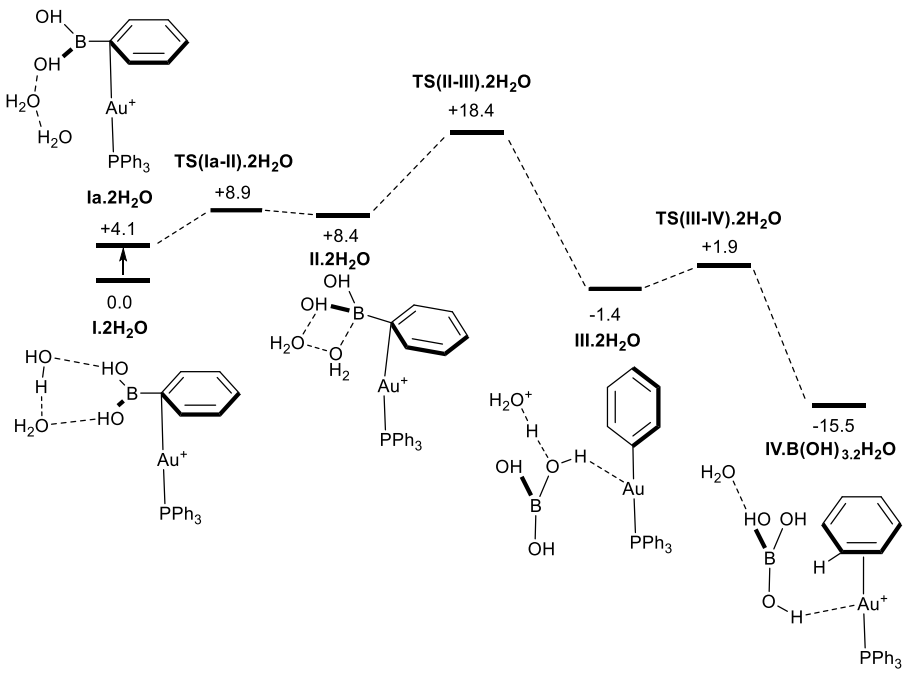


Figure 4.2: Computed free energy reaction profile for the protodeboronation of $PhB(OH)_2$ with two water molecules (D. Johnson and S. A. Macgregor).

Since significantly high barriers occurred with calculations involving one water molecule, calculations involving two, three or four water molecules were studied. If three or four water molecules were added, mechanisms and energies were similar to that of two water molecules. Thus, only the calculations involving the two water molecules are discussed. The two water molecules are thought to form a square-H array with the OH groups of the boronic acid **Ia.2H$_2$O** (*G* = 0.0 Kcal/mol). However, the initial mechanism is thought to start with the higher energy conformer of this species, **Ia.2H$_2$O** (*G* = +4.1 Kcal/mol), coordinating to Au(I) at the *ipso* carbon of the boronic acid in an η^1-type fashion. One water molecule then attacks the boron to form a weakly bound adduct **II.2H$_2$O** followed by the breaking of the B-C bond *via* **TS(II-III).2H$_2$O** (Figure 4.3) where the B-O bond length decreases and the B-C bond length increases to give **III.2H$_2$O**. This species has a σ-Ph ligand and a protonated boric acid-water cluster sitting above the phenyl ring with a short Au···H contact. The second water molecule is required to stabilise the proton released upon nucleophilic attack. Protodeboronation is then completed by rotation of the $B(OH)_2(H_2O)^+ \cdot H_2O$ moiety to a perpendicular position and delivery of a proton onto the *ipso*-C via **TS(III−IV)·2H$_2$O** (Figure 4.3). This proton transfer is aided by H-bonding to the external water molecule and leads to **IV·B(OH)$_3$·H$_2$O** in which a linear $(Ph_3P)Au(\eta^2\text{-}C_6H_6)$ complex interacts weakly with the $B(OH)_3 \cdot H_2O$ cluster. The rate

determining step of the reaction is therefore the breaking of the B-C bond with an energy barrier of 18.4 Kcal/mol.

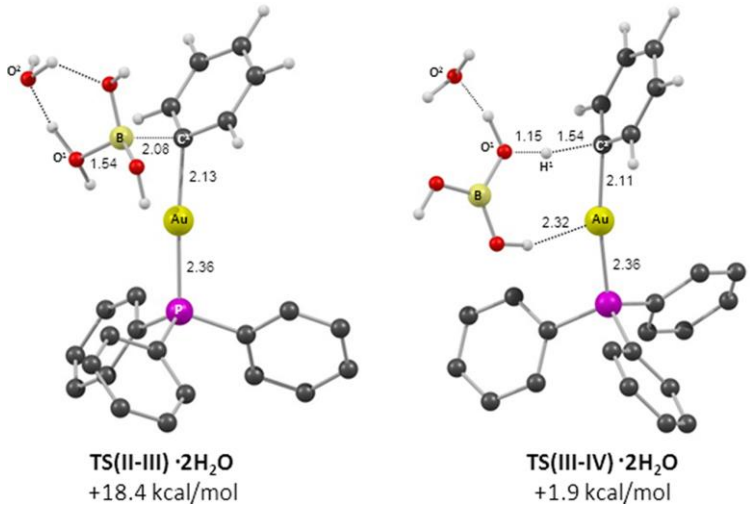
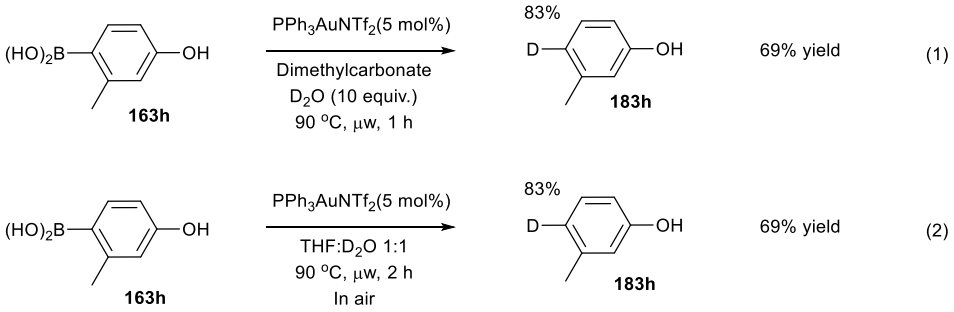


Figure 4.3: Computed structures of **TS(II−III)·2H2O** (B−C bond cleavage) and **TS(III−IV)·2H2O** (protonolysis). The phosphine-H have been deleted for clarity (D. Johnson and S. A. Macgregor).

4.4.3 Deuterodeboronation

In order to ascertain whether protodeauration was selective for the *ipso* position and to provide evidence to support the proposed mechanism, deuterodeboronation studies were carried out.



Scheme 4.14: Deuteration studies to prove *ipso*-selective proto(deutero)deauration

The reaction was carried out in dry dimethylcarbonate with 10 equivalents of D_2O added under strictly anhydrous conditions (Scheme 4.14, Eq. 1). Deuteration only occurred at the *ipso*-position with 83% D incorporated into the product, proving a regiospecific deauration step takes place. The reaction shown in Scheme 4.14, Equation 1, was carried out under anhydrous conditions in order to maximise the amount of deuterons incorporated into the product. In order to improve the practicality of the method, the amount of D_2O in the reaction was increased to a 1:1 THF:D_2O mixture and carried out

in air (Scheme 4.14, Eq. 2). The %D observed in the reaction shown in Scheme 4.14, Equation 2 was the same as that when carried out in under anhydrous conditions. This provided a practical, mild, acid- and base-free deuteration method, thus, a small substrate scope was carried out. The aryl boronic acids were dehydrated to the arylboroxines prior to reaction in order to ensure that no H_2O is released during the reaction. Addition of D_2O should form the required $ArB(OD)_2$ *in situ*.

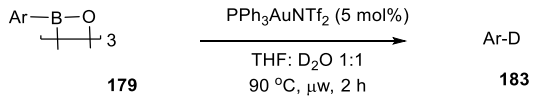
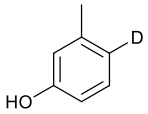
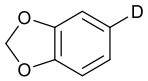
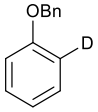
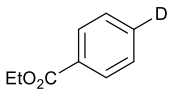
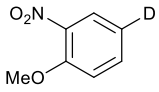
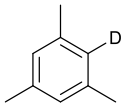
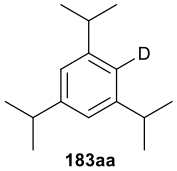
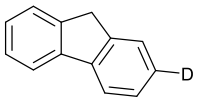
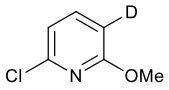
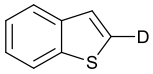
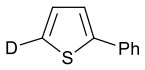
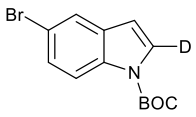


Table 4.6: Aryl boroxine acid scope

Entry	*d*-183	%deuteration[a]	Yield (%)[b]
1	 **183h**	83	70
2	 **183j**	100	98
3	 **183k**	100	88
4	 **183f**	100	<10%[c]
5	 **183t**	ND[d]	<15%[c]
6[e]	 **183y**	100	Quant.[c]

7	 **183aa**	40	ND[d]
8	 **183ab**	76	36
9[g]	 **183ad**	95	58
10	 **183ae**	96	93
11	 **183ag**	98	98
12[h]	 **183ah**	89	38

[a]Determined by ^{1}H NMR analysis. [b]Isolated yields. [c]Determined by ^{1}H NMR analysis of the crude with dimethylsulfone as internal standard. [d]Not determined. [e]Reaction done in d_8-THF. [f]3h. [g]4 h. [h]Molecular sieves added.

Electron rich boroxines (entries 2-3) deuterodeboronate effectively with 100% incorporation of deuterium within the product, with the exception boroxine **179h** where only 83% incorporation was observed (entry 1). In this case the phenolic proton may be causing the decrease in the % deuteration with H and D rapidly exchanging. Unlike protodeboronation, electron poor boroxines appear not to undergo deuterodeboronation effectively (entries 4-5). However, this deuteration method is complementary to that of the deuterodecarboxylation method where deuteration only occurred on electron poor substrates.[17-19] Boroxines which are slightly sterically hindered, such as that of boroxine **179y** (Table 4.6, entry 6) again perform well to again give 100% deuterated 1,3,5-trimethyl(2-*d*)benzene **183y**. However, upon increasing the steric hindrance of the boroxine the % of deuterium incorporated into the product decreases (40%, entry 7). However, heterocycles readily deuterodeboronate to give excellent %D incorporation into

the products with excellent yields (Table 4.6, entries 9-11), including a modest yield, 38%, of an acid sensitive BOC-protected indole (Table 4.6, entry 12).

4.5 Conclusions

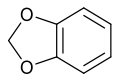
A mild gold(I) catalysed protodeboronation reaction has been successfully developed. The reaction can be carried out in "green" solvents and tolerates a wide variety of functional groups (including acid and base sensitive functional groups), which would not be tolerated with previously reported methods.

In the presence of D_2O, this technique can also be used as a mild, base- and acid free *ipso* deuteration of electron-rich and heterocyclic boronic acids. This method is complementary to that of the deuterodecarboxylation method which is limited to electron-withdrawing aryls.

4.6 Experimental

Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks. *J* values are given in Hz and s, bs, d, dd, ddd, dt, t, td, tt, q, qn, sext and m abbreviations correspond to singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublets, doublet of triplets, triplet, triplet of doublets, triplet of triplets quartet, quintet, sextet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained deposited neat or as a chloroform solution to a diamond/ZnSe plate. All boronic acids were purchased and used without further purification unless otherwise stated. Dimethylcarbonate was purchased and used without further purification. Dry THF (tetrahydrofuran) was obtained from a solvent purification system. CEM Microwave Discover was used for microwave heating, using sealed tubes and external surface sensor. The gold(I)-catalysed reactions were carried out without the need for dry solvents or inert atmosphere, unless stated otherwise.

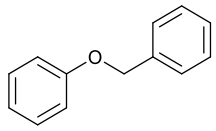
1,3-Benzodioxole (166j)[31]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 µl, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.8 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for 1 hour in the microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: 10:1 pentane/ether) to yield product **166j** as a colourless oil (62%, 15.7 mg, 0.103 mmol).

R_f 0.76 (5:1 pentane/ether); ν_{max} (cm^{-1}) 2924 (C-H), 2358, 2339 (O-CH_2-O), 1478, 1360 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (4H, m, Ar-H), 5.95 (2H, s, O-C<u>H$_2$</u>-O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.5 (C), 121.8 (CH), 108.8 (CH), 100.7 (CH_2).

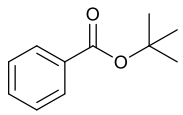
Benzyl phenyl ether (166j)[32]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 µl, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.8 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for 1 hour in the microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: 15:1 pentane/ether) to yield product **167j** as a white solid (93%, 34.7 mg, 0.189 mmol).

R_f 0.75 (5:1 pentane/ether); Mp: 42-43 °C ($CDCl_3$) [Lit.[33] 40 °C (Hexane)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12-7.30 (7H, m, Ar-H), 7.83-7.91 (3H, m, Ar-H), 4.97 (2H, s, O$C\underline{H_2}$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9 (C), 137.2 (C), 129.6 (CH), 128.7 (CH), 128.1 (CH), 127.6 (CH), 121.1 (CH), 115.0 (CH), 70.0 (CH_2); Found (FTMS + pAPCI) $[M + H]^+$ 185.0960, $C_{13}H_{13}O$ requires 185.0961.

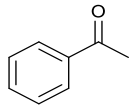
***tert*-Butyl 4-hydroxybenzoate (166o)[34]**



Boronic acid (0.2 mmol, 1.0 equiv.), $PPh_3AuNTf2$ (7.4 mg, 5 mol%), H_2O (0.04 ml, 2.0 mmol, 10 equiv.), dimethylcarbonate (0.8 ml, 0.25 M) and 1 bead of unactivated 4 Å molecular sieves were added to the microwave tube and heated at 90 °C for 1 hours in microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: 40:1 to 25:1 pentane/ether) to yield product **166o** as a colourless oil (30%, 11.0 mg, 0.06 mmol).

R_f 0.77 (5:1 pentane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97-8.02 (2H, m, Ar-H), 7.52 (1H, tt, *J* = 1.4, 6.5 Hz, Ar-H), 7.38-7.45 (1H, m, Ar-H), 1.60 (9H, s, *t*-Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 165.9 (C), 132.5 (CH), 132.2 (C),129.5 (CH), 128.3 (CH), 81.1 (C), 28.4 (CH_3); Found (GC/MS EI+) [M] 178.0989, $C_{11}H_{14}O_2$ requires 178.0990.

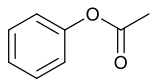
Acetophenone (166p)[35]



Boronic acid (0.220 mmol, 1 equiv.), PPh_3AuNTf_2 (5 mol%) and dimethyl carbonate (0.8 ml) were added to the microwave tube and placed in the microwave and heated at 90 °C for 2 hours. A second portion of PPh_3AuNTf_2 (5 mol%) was then added to the reaction mixture which was then heated in the microwave for a further 2 hours at 90 °C. The resulting mixture was then passed through a silica plug and washed with ether. The product was purified by column chromatography (eluent: 7:1 pentane/ether) to yield product **166p** as a colourless oil (65%, 17.2 mg, 0.14 mmol).

R_f 0.52 (5:1 pentane/ether); ν_{max} (cm^{-1}) 3062 (C-H), 1682 (C=O), 1598, 1582, 1448 (Ar C-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.94-7.98 (2H, m, Ar-H), 7.57 (1H, tt, *J* = 1.3, 6.3 Hz, Ar-H), 7.43-7.50 (2H, m, Ar-H), 2.61 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 198.3 (C), 137.3 (C), 133.2 (CH), 128.7 (CH), 128.4 (CH), 26.7 (CH_3).

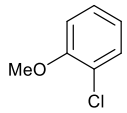
Phenyl acetate (166q)[36]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (0.04 ml, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.25 M) was added to microwave tube and heated in the microwave at 90 °C for 1 hour. The resulting mixture was passed through a silica plug and washed with ether. The product was purified by column chromatography (eluent: 15:1 pentane/ether) to yield product **166q** as a colourless oil (37%, 10.3 mg, 0.08 mmoles)

R_f 0.55 (5:1 pentane/ether); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.41 (2H, m, Ar-H), 7.20-7.26 (1H, m, Ar-H), 7.07-7.11 (2H, m, Ar-H), 2.30 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 169.6 (C), 150.8 (C), 129.6 (CH), 126.0 (CH), 121.7 (CH), 21.3 (CH_3); Found (FTMS + p APCI) $[M + H]^+$ 137.0594, $C_8H_9O_2$ requires 137.0597.

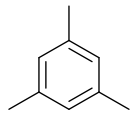
2-Chloroanisole (166u)[37]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 μl, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.8 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for 1 hour in the microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: 7:1 pentane/ether) to yield product **166u** as a colourless oil (47%, 13.6 mg, 0.097 mmol).

R_f 0.57 (5:1 pentane/ether); ν_{max} (cm^{-1}) 2940, 2838 (C-H), 1588, 1485, 1462, 1449 (Ar C-C), 1274 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (1H, dd, J = 1.6, 7.8 Hz, Ar-H), 7.20-7.25 (1H, m, Ar-H), 6.87-6.95 (2H, m, Ar-H), 3.90 (3H, s, OCH_3); ^{13}C (75.5 MHz, $CDCl_3$) δ 155.1 (C), 130.4 (CH), 127.9 (CH), 122.6 (C), 121.4 (CH), 112.2 (CH), 56.2 (CH_3).

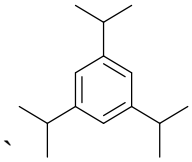
1,3,5-Trimethylbenzene (166y)[38]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 μl, 10 equiv.) and THF-d_8 (0.8 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for 1 hour in the microwave. Internal standard dimethylsulfone (9.4 mg, 0.5 equiv.) was added to the mixture. ^1H NMR yield of 95% was obtained. Due to the volatile nature of the product, an isolated yield was not obtained.

^1H NMR (300 MHz, THF-d_8) δ 6.24 (3H, s, Ar-H), 1.72 (9H, s, CH_3).

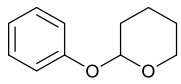
1,3,5-Trisopropylbenzene (166aa)[39]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 µl, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.8 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for **3 hours** in microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: pentane) to yield product **166aa** as a colourless oil (99%, 37.8 mg, 0.18 mmol).

R_f 0.86 (5:1 pentane/ether); ν_{max} (cm^{-1}) 2957 (C-H), 1599, 1465, 1381 (Ar C-C) ;^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96 (3H, s, Ar-H), 2.92 (3H, sept, *J* = 6.9 Hz, $CH_3C\underline{H}CH_3$), (18H, d, *J* = 6.9 Hz, $C\underline{H_3}CHC\underline{H_3}$); ^{13}C (75.5 MHz, $CDCl_3$) δ 148.8 (C), 122.2 (CH), 34.4 (CH), 24.3 (CH_3).

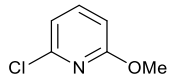
2-Phenoxytetrahydro-2H-pyran (166ac)[40]



Boronic acid (0.2 mmol), PPh_3AuNTf_2 (7.4 mg, 5 mol%), unactivated powdered 4 Å molecular sieves (20 mg), H_2O (40 µl, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.8 ml) were added to a microwave tube and heated in the microwave at 90 °C for **4 hours**. The resulting mixture was passed through an alumina plug and washed with ether. The product was purified by column chromatography (alumina used, eluent: 25:1 pentane/ether) to yield product **166ac** as a colourless oil (83%, 29.2 mg, 0.164 mmol).

R_f 0.88 (5:1 pentane/ether, alumina TLC plate); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.31 (2H, m, Ar-H), 7.04-7.09 (2H, m, Ar-H), 6.96-7.01 (1H, m, Ar-H), 5.43 (1H, t, *J* = 3.3 Hz, OC<u>H</u>O), 3.87-3.97 (1H, m, OCH_2), 3.57-3.65 (1H, m, OCH_2), 1.97-2.07 (1H, m, Alkyl-H), 1.84-1.90 (2H, m, Alkyl-H), 1.57-1.73 (3H, m, Alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 157.2 (C), 129.5 (CH), 121.7 (CH), 116.6 (CH), 96.5 (CH), 62.2 (CH_2), 30.6 (CH_2), 25.4 (CH_2), 19.0 (CH_2); Found (GC/MS EI+) $[M]^+$ 178.0993, $C_{11}H_{14}O_2$ requires 178.0994.

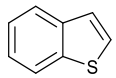
2-Chloro-6-methoxypyridine (166ad)[41]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 µl, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.8 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for **3 hours** in the microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: 15:1 pentane/ether) to yield product **166ad** as a colourless oil (72%, 16.9 mg, 0.118 mmol).

R_f 0.70 (5:1 pentane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, dd, *J* = 7.5, 8.2 Hz, CHC<u>H</u>CH), 6.90 (1H, dd, *J* = 0.7, 7.5 Hz, ClCC<u>H</u>), 6.65 (1H, dd, *J* = 0.7, 8.2 Hz, C<u>H</u>COMe), 3.94 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.0 (C), 148.5 (C), 140.6 (CH), 116.4 (CH), 109.2 (CH), 54.1 (CH_3); Found (FTMS + pNSI) $[M + H]^+$ 144.0207, C_6H_7ClNO requires 144.0211.

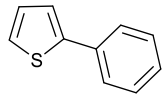
1-Benzothiophene (166ae)[42]



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 µl, 2.0 mmol, 10 equiv.) and dimethylcarbonate (0.8 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for 1 hour in the microwave. The resulting mixture was passed through a silica plug, washed with pentane and then concentrated to yield product **166ae** as a colourless oil (100%, 27.5 mg, 0.2 mmol). Note: the product begins to decompose if left on silica.

^{1}H (300 MHz, $CDCl_3$) δ 7.77-7.82 (1H, m, Ar-H), 7.71-7.76 (1H, m, Ar-H), 7.33 (1H, d, *J* = 5.4 Hz, Ar-H), 7.21-7.29 (3H, m, Ar-H); ^{13}C (75.5 MHz, $CDCl_3$) δ 139.8 (C), 139.7 (C), 126.4 (CH), 124.31 (CH), 124.26 (CH), 124.0 (CH), 123.7 (CH), 122.6 (CH); Found (FTMS + p APCI) $[M + H]^+$ 135.0262, C_8H_7S requires 135.0263.

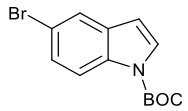
2-Phenylthiophene (166ag)[43]



Boronic acid (0.1 mmol, 1.0 equiv.), PPh_3AuNTf_2 (3.7 mg, 5 mol%), H_2O (20 µl, 1.0 mmol, 10 equiv.) and dimethylcarbonate (0.4 ml, 0.25 M) were added to the microwave tube and heated at 90 °C for 1 hour in the microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: pentane) to yield product **166ag** as a colourless oil (85%, 13.7 mg, 0.09 mmol).

R_f 0.78 (5:1 pentane/ether); ^{1}H (300 MHz, $CDCl_3$, referenced to TMS) δ 7.51-7.55 (2H, m, Ar-H), 7.26-7.33 (2H, m, Ar-H), 7.16-7.24 (3H, m, Ar-H), 7.00 (dd, 1H, *J* = 3.6, 5.1 Hz, Ar-H); ^{13}C (75.5 MHz, $CDCl_3$) δ 144.6 (C), 134.6 (C), 129.0 (CH), 128.1 (CH), 127.6 (CH), 126.1 (CH), 124.9 (CH), 123.2 (CH); Found (FTMS + p APCI) $[M + H]^+$ 161.0414, $C_{10}H_9S$ requires 161.0419.

***N*-Boc-5-Bromoindole (166ah)[44]**



Boronic acid (0.2 mmol, 1.0 equiv.), PPh_3AuNTf_2 (7.4 mg, 5 mol%), H_2O (40 µl, 2.0 mmol, 10 equiv.), dimethylcarbonate (0.8 ml, 0.25 M) and 1 bead of unactivated 4 Å molecular sieves were added to the microwave tube and heated at 90 °C for **3 hours** in microwave. The resulting mixture was passed through a silica plug, washed with ether and then concentrated. The product was purified by column chromatography (eluent: 15:1 pentane/ether) to yield product **166ah** as colourless oil (73%, 42.1 mg, 0.142 mmol).

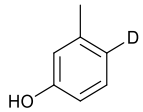
R_f 0.67 (5:1 pentane/ether); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (1H, d, *J* = 8.8 Hz, BrCCHC<u>H</u>CN), 7.69 (1H, d, *J* = 2.3 Hz, BrCC<u>H</u>C), 7.59 (1H, d, *J* = 3.7 Hz, C<u>H</u>CHNBOC), 7.40 (1H, dd, *J* = 2.3, 8.8 Hz, BrCC<u>H</u>CHCN), 6.50 (1H, d, *J* = 3.7 Hz, CHC<u>H</u>NBOC), 1.67 (9H, s, *t*-butyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.5 (C), 134.1 (C), 132.4 (C), 127.1 (CH x 2), 123.6 (CH), 116.7 (CH), 116.1 (C), 106.6 (CH), 84.2 (C), 28.3 (CH_3); Found (FTMS + pAPCI) $[M + H]^+$ 296.0275, $C_{13}H_{15}BrNO_2$ requires 296.0281.

Deuterodeboronation

General procedure A

Boroxine (0.2 mmol), dry THF (0.4 ml) and D_2O (0.4 ml) were added to the microwave tube followed by PPh_3AuNTf_2 (7.4 mg, 5 mol%) and heated in the microwave at 90 ^oC for 2 hours. The resulting mixture was passed through a plug of silica and washed with ether. The products were purified by column chromatography (eluent: pentane/ether).

3-Methyl-(4-*d*)phenol (*d*-183h)



General procedure A was followed to yield product ***d*-183h** (83% deuteration) as a colourless oil (70%, 15.3 mg, 0.139 mmol). Purified by column chromatography (eluent: 5:1 pentane/ether).

R_f 0.26 (5:1 pentane/ether); ν_{max} (cm^{-1}) 3311 (O-H), 2921 (C-H), 2250 (C-D), 1584, 1473, 1448 (Ar C-C), 1240 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.10-7.16 (1H, m, Ar-H), 6.62-6.67 (2H, m, Ar-H), 4.76 (1H, s, OH), 2.32 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 139.9 (C), 129.4 (CH), 121.8 (C, t, J = 24.4 Hz), 116.1 (CH), 112.3 (CH), 21.4 (CH_3); Found (FTMS + pAPCI) $[M + H]^+$ 110.0708, C_7H_8DO requires 110.0711.

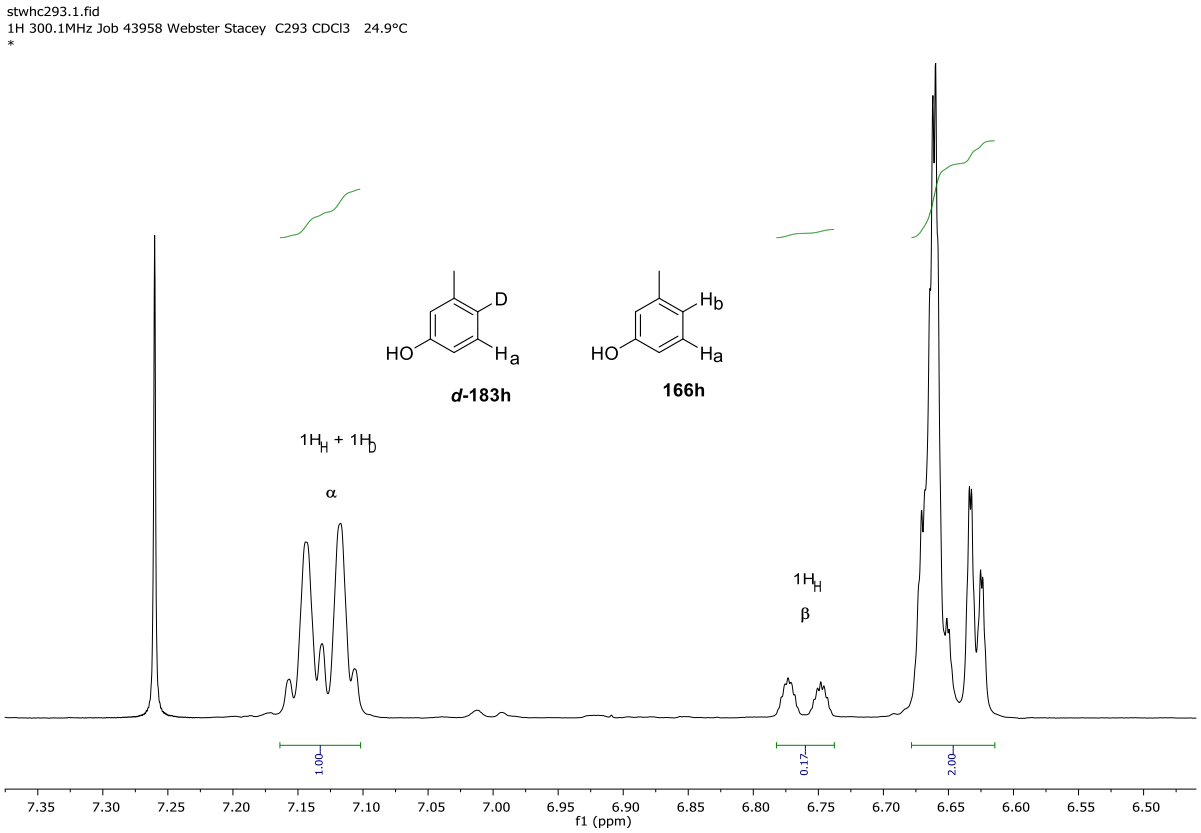
$$At\ 100\%\ D \quad \beta = \beta_{100} = 0$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 1$$

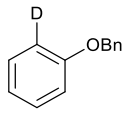
$$\therefore \%\ D = (1 - \beta) \times 100$$

$$\therefore \%\ D = (1 - 0.17) \times 100$$

$$\therefore \%\ D = 83\%$$



1-(Benzyloxy)benzene-2-*d* (*d*-183k)



General procedure A was followed to yield product ***d*-183k** (100% deuteration) as a white solid (88%, 33.4 mg, 0.183 mmol). Purified by column chromatography (eluent: 15:1 pentane/ether).

R_f 0.80 (5:1 pentane/ether); Mp: 38-39 °C ($CDCl_3$); ν_{max} (cm^{-1}) 3064, 3030 (C-H), 2869 (C-D), 1589, 1474, 1462, 1452, 1444 (Ar C-C), 1230 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$, referenced using TMS) δ 7.14-7.40 (7H, m, Ar-H), 6.84-6.93 (2H, m, Ar-H), 4.97 (2H, s, OCH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 158.9 (C), 137.2 (C), 129.6 (CH), 129.5 (CH), 128.7 (CH), 128.1 (CH), 127.6 (CH), 121.1 (CH), 115.0 (CH), 114.7 (C, t, J = 24.4 Hz) 70.0 (CH_2); Found (GC/MS EI) $[M]^+$ 185.0951, $C_{13}H_{11}DO$ requires 185.0955.

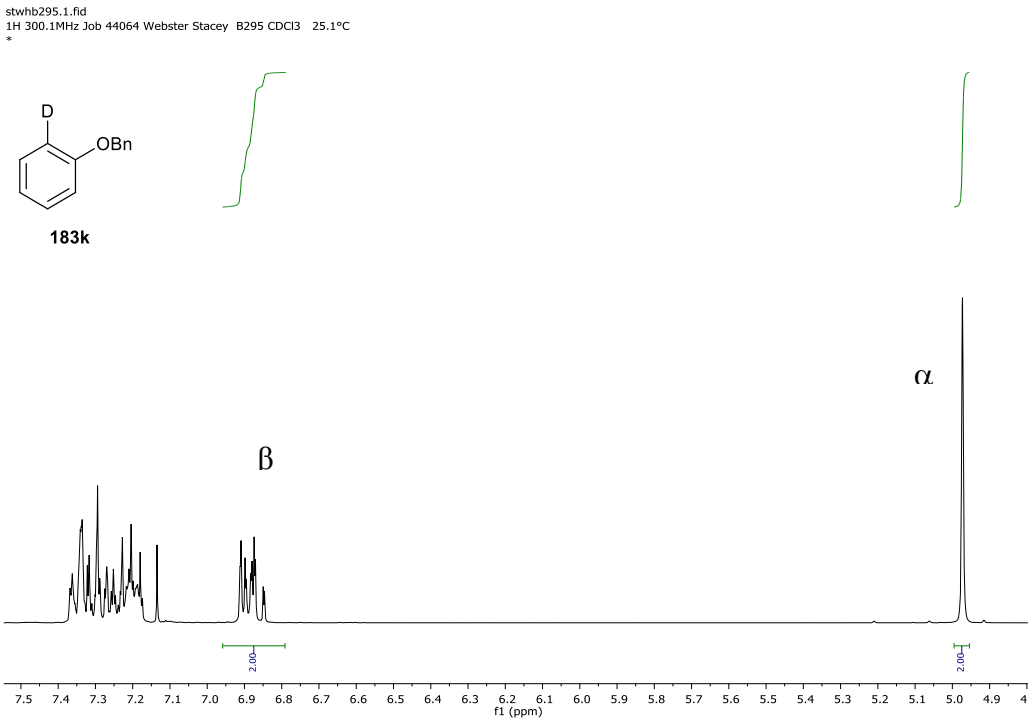
$$At\ 100\%\ D \quad \beta = \beta_{100} = 2$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 3$$

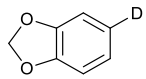
$$\therefore \%\ D = (3 - \beta) \times 100$$

$$\therefore \%\ D = (3 - 2) \times 100$$

$$\therefore \%\ D = 100\%$$



Benzo[*d*][1,3]dioxole-5-*d* (*d*-183j)



General procedure A was followed with the exception that the silica plug was washed with pentane and then 10:1 pentane ether to yield product ***d*-183j** (100% deuteration) as a colourless oil (98%, 23.7 mg, 0.193 mmol).

ν_{max} (cm^{-1}) 2891 (C-H), 1500, 1474, 1442 (Ar C-C), 1229 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.83 (3H, m, Ar-H), 5.95 (2H, s, OCH_2O); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.5 (2 x C), 121.6 (CH), 121.5 (C, t, J = 24.8 Hz), 108.8 (CH), 108.7 (CH), 100.7 (CH_2); Found (FTMS + pAPCI) $[M - H]^+$ 122.0344, $C_7H_4DO_2$ requires 122.0347.

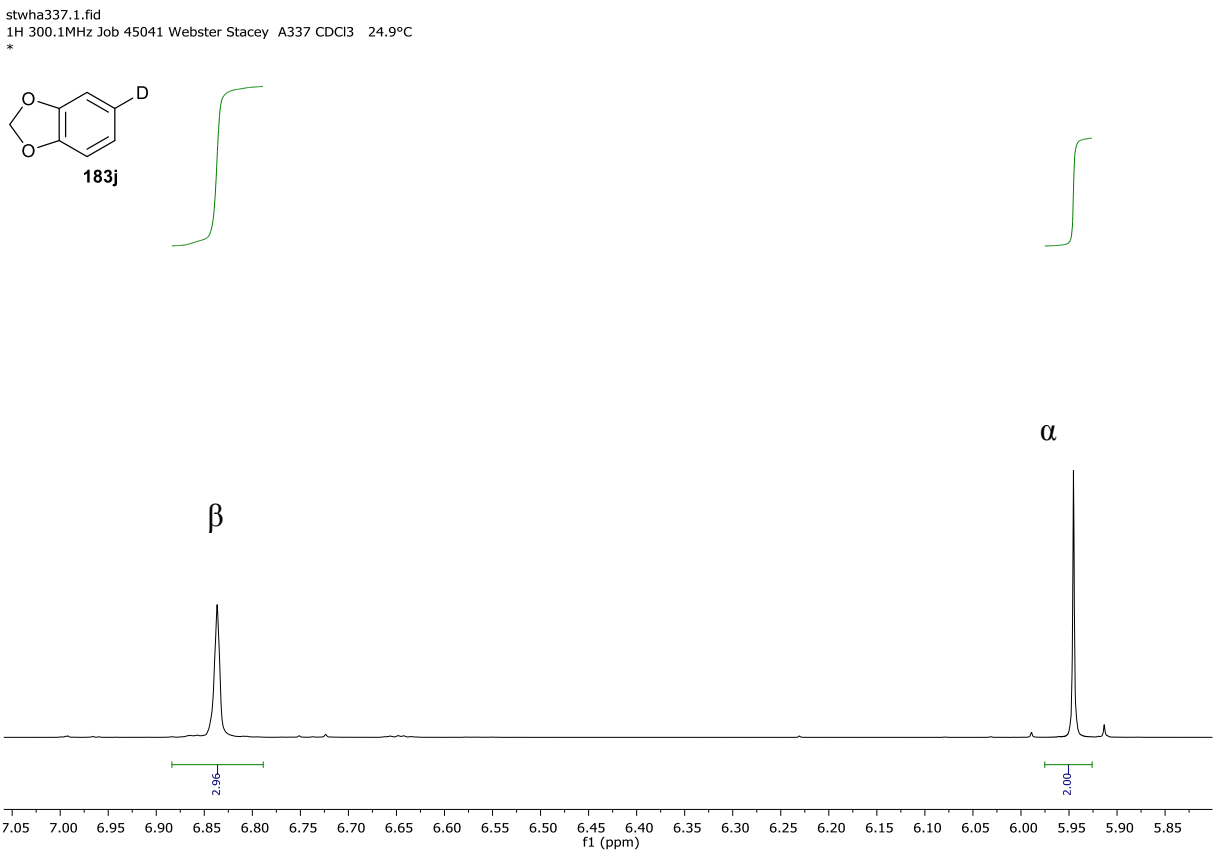
$$At\ 100\%\ D \quad \beta = \beta_{100} = 3$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 4$$

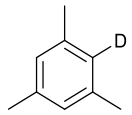
$$\therefore \%\ D = (4 - \beta) \times 100$$

$$\therefore \%\ D = (4 - 2.96) \times 100$$

$$\therefore \%\ D = 104\%$$



1,3,5-Trimethyl(2-*d*)benzene (*d*-183y)



General procedure A was followed but THF-d_8 was used instead of THF and no silica plug was used. Instead an internal standard dimethylsulfone (9.4 mg, 0.5 equiv) was added to the reaction mixture which was then dried with $MgSO_4$. ^1H NMR analysis indicated quantitative yield and the product ***d*-183y** was 100% deuterated. The product was not isolated due to its volatility.

^1H NMR (300 MHz, THF-d_8) δ 6.24 (3H, s, Ar-H), 1.72 (9H, s, CH_3).

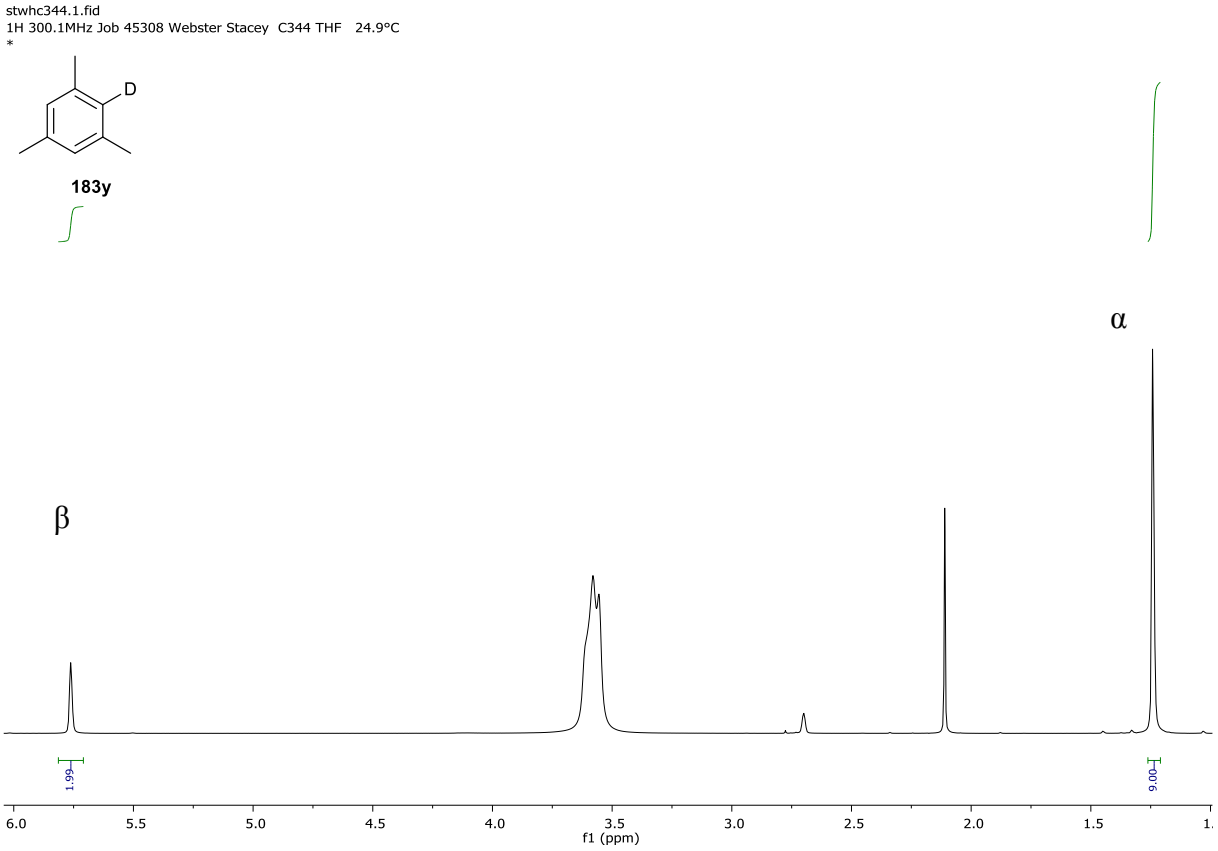
$$At\ 100\%\ D \quad \beta = \beta_{100} = 2$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 3$$

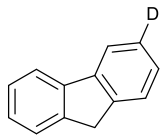
$$\therefore \%\ D = (3 - \beta) \times 100$$

$$\therefore \%\ D = (3 - 1.99) \times 100$$

$$\therefore \%\ D = 101\%$$



9*H*-Fluorene-3-*d* (*d*-183ab)



General procedure A was followed with the exception that the silica plug was washed with pentane and then 30:1 pentane ether to yield product ***d*-183ab** (76% deuteration) as a yellow solid (36%, 12.0 mg, 0.07 mmol).

Mp: 111-113 ^{o}C; ν_{max} (cm^{-1}) 2891 (C-H), 1500, 1474, 1442 (Ar C-C), 1229 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 7.8 Hz Ar-H), 7.54-7.58 (2H, m, Ar-H), 7.35-7.42 (2H, m, Ar-H), 7.31 (1H, td, *J* = 7.4, 1.3 Hz, Ar-H), 3.91 (2H, s, CH_2); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 143.5 (C), 141.8 (C), 126.9 (CH), 126.8 (CH), 126.6 (C, t, *J* = 24.4 Hz), 125.2 (CH), 125.1 (CH), 120.0 (CH), 37.1 (CH_2); Found (FTMS + pAPCI) $[M - H]^+$ 166.0758, $C_{13}H_8D$ requires 166.0762.

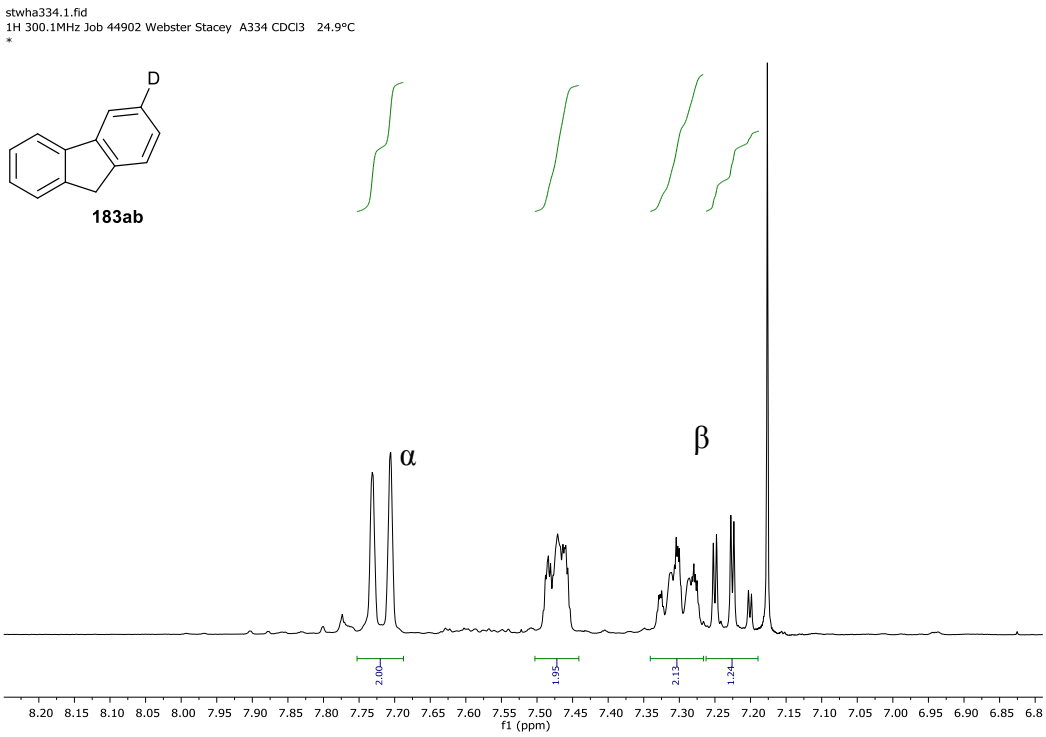
$$At\ 100\%\ D \quad \beta = \beta_{100} = 1$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 2$$

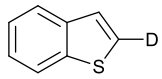
$$\therefore \%\ D = (2 - \beta) \times 100$$

$$\therefore \%\ D = (2 - 1.24) \times 100$$

$$\therefore \%\ D = 76\%$$



Benzo[*b*]thiophene-2-*d* (*d*-183ae)[17]



General procedure A was followed with the exception that the silica plug was washed with pentane instead of ether to yield product ***d*-183ae** (96% deuteration) as a colourless oil (93%, 25.6 mg, 0.190 mmol). Note that the product begins to decompose if left on silica.

ν_{max} (cm^{-1}) 3059 (C-H), 2248 (C-D), 1466, 1447 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89-7.94 (1H, m, Ar-H), 7.83-7.87 (1H, m, Ar-H), 7.33-7.42 (3H, m, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.8 (C), 139.7 (C),126.2 (C, t, J = 28.2 Hz), 124.31 (CH), 124.28 (CH), 123.8 (CH), 123.7 (CH), 122.6 (CH); Found (FTMS + p APCI) $[M]^+$ 135.0246, C_8H_5DS requires 135.0247. Mass spectrometry calculated 95% deuteration which is consistent with NMR data.

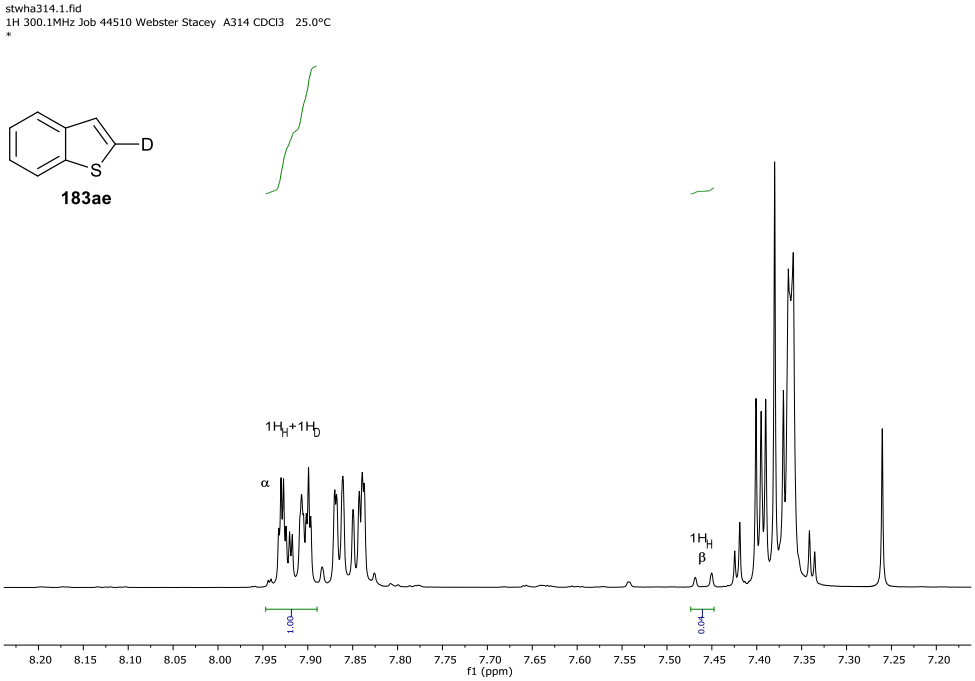
$$At\ 100\%\ D \quad \beta = \beta_{100} = 0$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 1$$

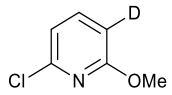
$$\therefore \%\ D = (1 - \beta) \times 100$$

$$\therefore \%\ D = (1 - 0.04) \times 100$$

$$\therefore \%\ D = 96\%$$



2-Chloro-6-methoxypyridine-5-*d* (*d*-183ad)



General procedure A was followed with the exception of reaction time which was extended to 4 hours rather than 2 to yield product ***d*-183ad** (95% deuteration) as a colourless oil (58%, 16.5 mg, 0.114 mmol). Purified by column chromatography (eluent: 15:1 pentane/ether).

R_f 0.78 (5:1 pentane/ether); ν_{max} (cm^{-1}) 2954 (C-H), 1587, 1574, 1552 (C-C Ar), 1259 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, dt, *J* = 1.0, 7.5 Hz, Ar-H), 6.89 (1H, d, *J* = 7.5 Hz, Ar-H), 3.94 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 164.0 (C), 148.5 (C), 140.5 (CH), 116.3 (CH), 109.0 (C, t, *J* = 25.6 Hz), 54.1 (CH_3); Found (FTMS + p NSI) $[M + H]^+$ 145.0271, C_6H_6DClO requires 145.0273.

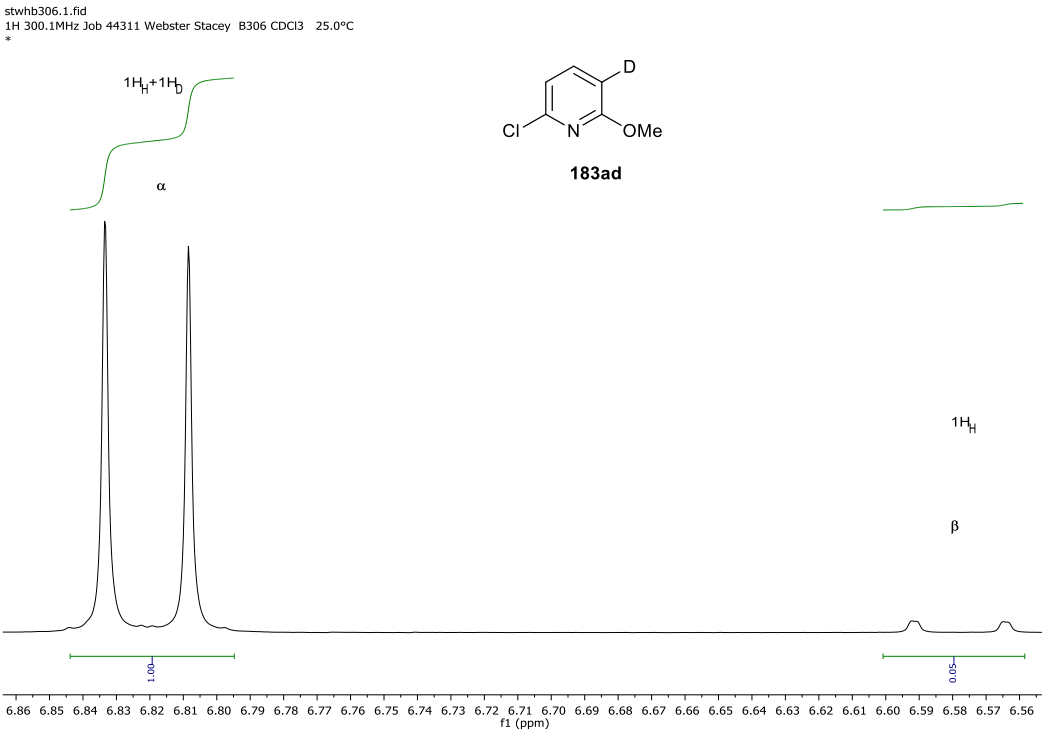
$$At\ 100\%\ D \quad \beta = \beta_{100} = 0$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 1$$

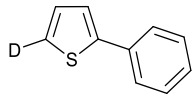
$$\therefore \%\ D = (1 - \beta) \times 100$$

$$\therefore \%\ D = (1 - 0.05) \times 100$$

$$\therefore \%\ D = 95\%$$



2-Phenylthiophene-5-*d* (*d*-183ag)



General procedure A was followed but on a smaller scale (0.1 mmol compared to 0.2 mmol) and silica plug was washed with pentane to yield product ***d*-183ag** (98% deuteration) as a colourless oil (98%, 16.0 mg, 0.099 mmol).

ν_{max} (cm^{-1}) 3073 (C-H), 2324 (C-D) 1599, 1530, 1485, 1445, 1420 (C-C Ar); ^{1}H NMR (300 MHz, d_6-Acetone) δ 7.64-7.69 (2H, m, Ar-H), 7.37-7.46 (3H, m, Ar-H), 7.30 (1H, tt, J = 1.3, 6.7 Hz, Ar-H), 7.12 (1H, d, J = 3.6 Hz, Ar-H) ; ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.5 (C), 134.6 (C), 129.0 (CH), 128.0 (CH), 127.6 (CH), 126.1 (CH), 124.9 (C, t, J = 14.7 Hz), 123.2 (CH); Found (FTMS + p APCI) $[M + H]^+$ 161.0400, $C_{10}H_7S$ requires 161.0404.

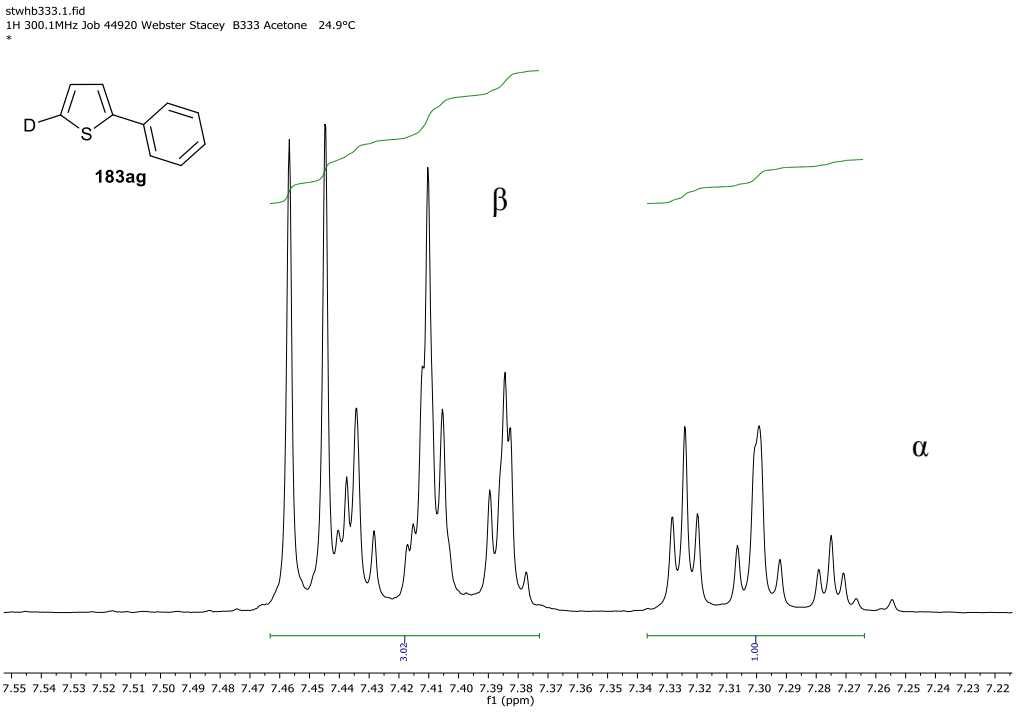
$$At\ 100\%\ D \quad \beta = \beta_{100} = 3$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 4$$

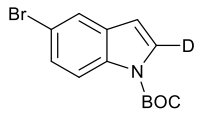
$$\therefore \%\ D = (4 - \beta) \times 100$$

$$\therefore \%\ D = (4 - 3.02) \times 100$$

$$\therefore \%\ D = 98\%$$



***tert*-Butyl-5-bromo-1*H*-indole-1-carboxylate-2-*d* (*d*-183ah)**



General procedure A was followed with the exception that 1 bead of unactivated 4 Å molecular sieves were added to yield product ***d*-183ah** (89% deuteration) as a colourless oil (38%, 19.5 mg, 0.07 mmol). Purified by column chromatography (eluent 15:1 pentane/ether).

R_f 0.76 (5:1 pentane/ether); ν_{max} (cm^{-1}) 2978 (C-H), 1732 (C=O) 1572, 1509, 1476, 1438 (C-C Ar); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.02 (1H, d, *J* = 8.8 Hz, Ar-H), 7.67 (1H, dd, *J* = 0.4, 2.0 Hz, Ar-H), 7.39 (1H, dd, *J* = 2.0 Hz, 8.8 Hz, Ar-H), 6.50 (1H, d, *J* = 0.4 Hz, Ar-H), 1.67 (9H, s, *t*-butyl); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.5 (C), 134.1 (C), 132.4 (C), 127.1 (CH), 123.7 (CH), 116.7 (CH), 116.1 (C), 106.4 (CH), 84.3 (C), 28.3 (CH_3), The carbon attached to the deuterium atom could not be observed by NMR. However, both proton NMR and mass spectrometry data suggest they desired product is formed; Found (FTMS + p APCI) $[M + H]^+$ 299.0320, $C_{13}H_{14}DBrNO_2$ requires 299.0323

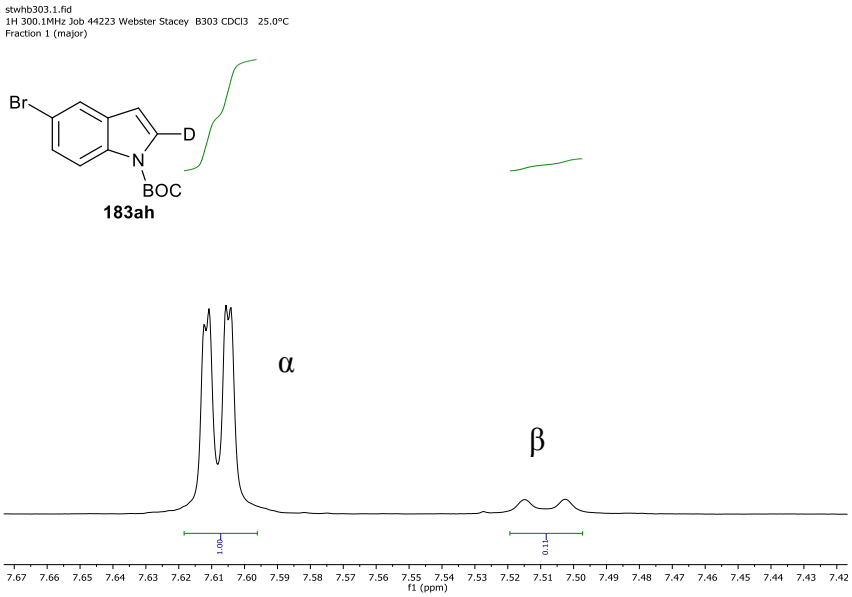
$$At\ 100\%\ D \quad \beta = \beta_{100} = 0$$

$$At\ 0\%\ D \quad \beta = \beta_0 = 1$$

$$\therefore \%\ D = (1 - \beta) \times 100$$

$$\therefore \%\ D = (1 - 0.11) \times 100$$

$$\therefore \%\ D = 89\%$$



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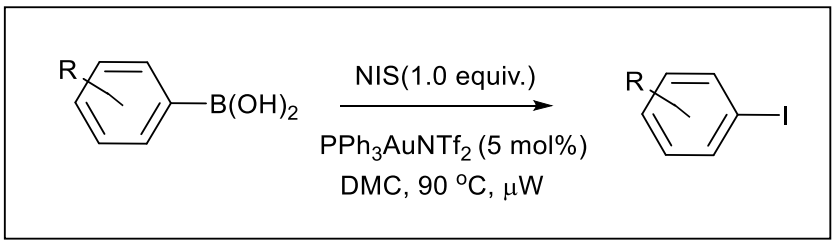
Chapter 5: Iododeboronation of Boronic Acids



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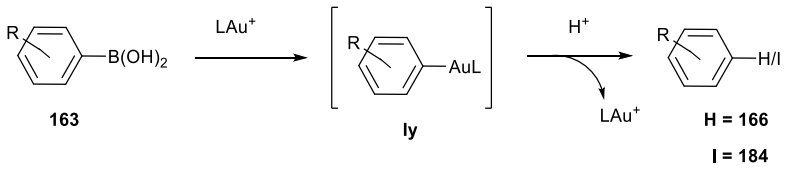
5.1 Introduction

The Lee group have successfully shown the proto- and deuterodeboronation of boronic acids *via* an organogold species, Scheme 5.1 (Chapter 4). Following these results, it was speculated whether an electrophile, such as I^+, could react with the organogold species **Iy** to form aryl iodides regioselectively at the *ipso* position. Therefore, a brief discussion on the iodination of boronic acids will be given here.



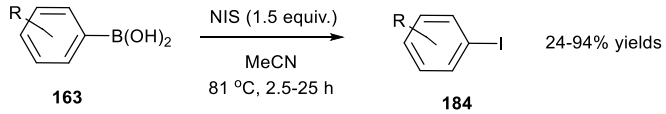
Scheme 5.1: Previous protodeboronation work

Aryl iodides are highly useful, synthetic intermediates as they can be used in many synthetic reactions, such as coupling reactions, both with and without transition metals.[1] The use of aryl iodides is usually preferred over the use of aryl bromides or chlorides as they are known to show a much higher degree of reactivity.[2] In recent years, aryl iodides have increasing applications in medical imaging as radiolabelled pharmaceuticals.[3]

Radiolabelling reactions need to be rapid and efficient, with the radiopharmaceutical being obtained in high radiochemical yield and purity. There are a number of factors which need to be taken into account when choosing a radiolabelling technique including the stability and reactivity of the precursor, precursor toxicity, ease of precursor synthesis, and purification of the final product from the precursor.[3]

For these reasons, a number of different methods for preparing aryl iodides have been developed. These methods include electrophilic aromatic substitution with iodine, the Sandmeyer reaction[4] and various other methods. However, these methods usually require harsh conditions and the use of toxic metals.

In 1997 Olah and co-workers developed a mild method for the preparation of haloarenes by *ipso*-substitution of aryl boronic acids with *N*-halosuccinimides.[5] They were able to synthesise several *ipso*-substituted iodoarenes in good yields with various functionalities (Scheme 5.2).



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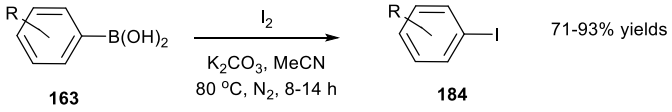
R = H, OMe, Cl, Br, CHO

Scheme 5.2: Metal free iodination of boronic acids by Olah.

This reaction works well for electron-rich and slightly electron-poor boronic acids, but poor yields were observed for the 3-nitrophenylboronic acid. Although no metal catalyst is needed, the reaction requires high temperatures of 80 °C, long reaction times (2.5-25 hours) and the use of acetonitrile as a solvent.[5]

In 2014, Fu and co-workers published a paper investigating the iodination of arylboronic acids (Scheme 5.3).[6] Once again, high temperatures and long reaction times were needed. In order for this reaction to proceed efficiently, high purity K_2CO_3 is required and the reaction had to be carried out under anhydrous conditions. However, unlike the work carried out by Olah, this reaction tolerates a wide variety of functional groups including electron-rich and electron-poor boronic acids containing carboxylic acids, esters, amines, ketones and aldehydes.



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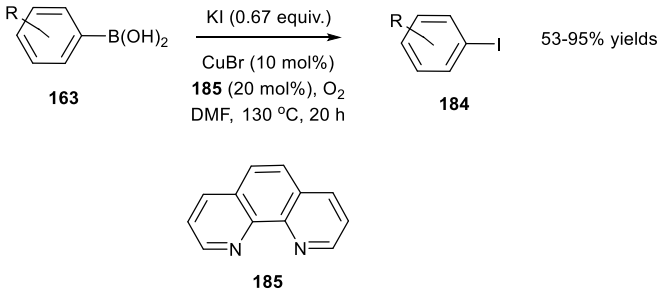
Scheme 5.3: Metal free iodination of boronic acids by Fu.

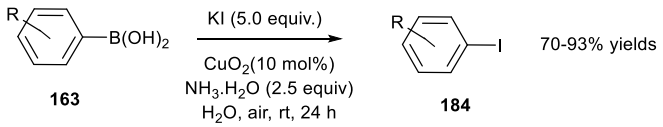
Further to this, Lupattelli and co-workers also investigated the *ipso*-iodination of boronic acids. Although reaction times are decreased to 1 hour, they still require temperatures of 80 °C, an additive (KF) and the reaction has to be carried out in 1,4-dioxane. However, the reaction tolerates both electron-rich and electron-poor boronic acids as well as heterocycles.[7]

Boronic acids can also be transformed to aryl halides through the use of a copper catalyst. By using $CuBr_2$ with ligand **185**, Zhang *et al.* successfully developed a regiospecific iodination reaction which tolerated a wide range or boronic acids using KI as their source of I^- (Scheme 5.4). Once again the reaction was only efficient at high temperatures and required long reaction times. Further to this, the reaction only produced good yields when using DMF as a solvent and had to be carried out in an oxygen rich atmosphere.[8]



Scheme 5.4: Cu-catalysed iodination of boronic acids by Zhang.

Before developing the metal-free iododeboronation reaction, Fu and co-workers also investigated copper-catalysed reactions (Scheme 5.5). They were able to develop a very mild transformation which tolerated a wide variety of functional groups including aldehydes, alcohols, esters and carboxylic acids in good to excellent yields. Unlike other iododeboronation reactions, this particular set of conditions could be carried out in water at room temperature and there was no need to exclude air. However, in order for the reaction to produce good yields long reaction times and the presence of a base were required.[9]

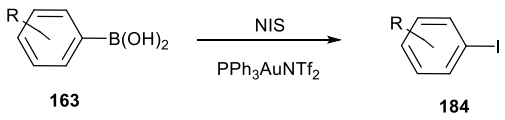


Scheme 5.5: Cu-catalysed iodination of boronic acids by Fu.

To summarise, the iododeboronation of boronic acids to form aryl halides can be achieved by both metal free and metal-catalysed methods. However, both of these methods suffer from drawbacks such as long reaction times, environmentally damaging solvents, the need for additives and occasionally must be carried out under inert conditions. Therefore, a mild method for the preparation of aryl iodides which could be carried out in "green" solvents without the need for additives or long reaction times would be advantageous.

5.2 Project Aims

Based on our previous work investigating the proto- and deuterodeboronation of boronic acids, it was speculated whether an electrophile, such as I^+, could react with the boronic acid under gold(I) catalysis to generate aryl iodides regiospecifically at the *ipso*-position (Scheme 5.6).



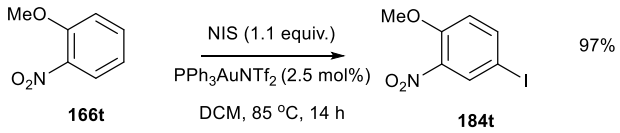
Scheme 5.6: Project Aim.

We therefore set out to develop a procedure that is:-

i) More environmentally friendly, using "green" solvents.

ii) With a much shorter reaction time, which may be useful for applications in radiolabelling studies.

It should be noted that gold(I) can also catalyse the iodination of arenes *via* a Friedel-Crafts-type mechanism in which PPh_3AuNTf_2 activates the NIS and enhances its reactivity (Scheme 5.7).[10] Therefore, overiodination could be potentially problematic in this project and each crude NMR should be carefully analysed to identify products.



Scheme 5.7: Gold(I)-catalysed iodination of arenes by Frontier *et al*.

5.3 Previous work

Initial optimisation studies carried out by Conor Fletcher (BSc student) showed that dimethylcarbonate was the most effective solvent for the reaction and to achieve good yields of the aryl iodides, temperatures of 90 °C were required. All reactions could be carried out in air without the need for dry solvents. Reactions were carried out in a microwave reactor.

5.4 Results and Discussion

5.4.1 Optimsation

Prior to the substrate scope, further optimisation studies were carried out in order to determine whether shorter reaction times could be achieved (Table 5.1).

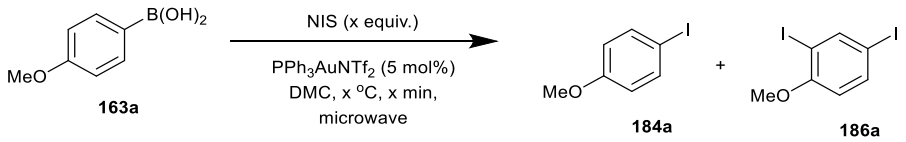


Table 5.1: Optimisation

Entry	Temp (°C)	Time (mins)	Equiv. NIS	Yield (%)[a]	**184a**:**186a**
1	70	10	1.1	93	3:1
2	90	10	1.1	100	6:1
3	100	5	1.1	91	10:1
4	100	2	1.1	99	9:1
5	**90**	**5**	**1.0**	**92**	**18:1**
6	100	5	1.0	88	19:1

[a]Combined yield of **184a** and **186a**.

As our original conditions began with temperatures of 90 °C for 60 mins, the time was reduced to 10 mins at 90 °C in order to establish whether shorter reaction times were possible (entry 2). At 10 mins, a quantitative yield was observed, however, a 6:1 ratio of **184a**:**186a** was obtained (entry 2). In order to try and reduce the yield of the overiodinated side product, the temperatures were decreased to 70 °C (entry 1). Although an excellent yield was still obtained, interestingly more of the overiodinated product was observed (entry 1). Based on this observation, temperatures were then increased to 100 °C for 5 mins where a better ratio of **184a**:**186a** 10:1 was obtained (entry 3). In order to

further improve the ratio of **184a**:**186a**, a shorter reaction time of 2 mins was investigated (entry 4), however, no improvement was observed. Therefore, the equivalents of NIS was reduced from 1.1 equiv. to 1.0 equiv. (entries 5-6). Upon decreasing the equivalents of NIS, an excellent ratio of 18:1 was obtained at 90 °C for 5 mins (entry 5). These conditions were then used to investigate the substrate scope.

5.4.2 Substrate Scope

Next a substrate scope was carried out (Table 5.2).

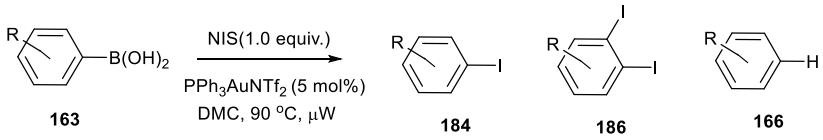
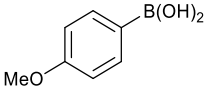
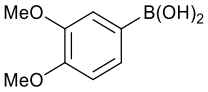
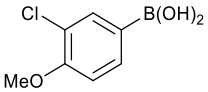
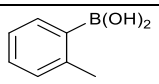
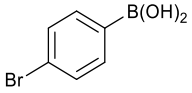
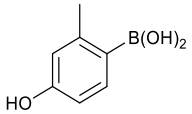
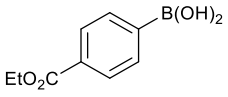
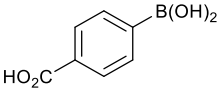
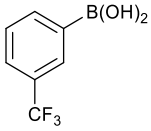
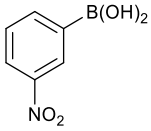
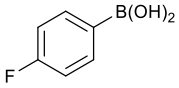
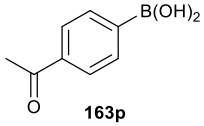
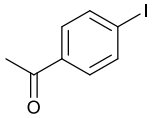
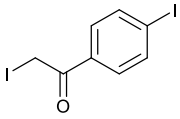
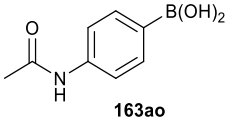
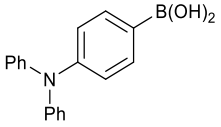
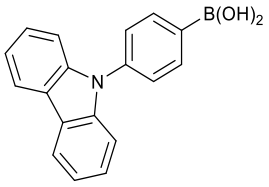
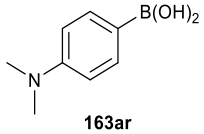
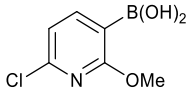
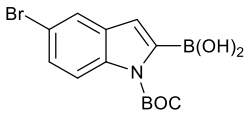
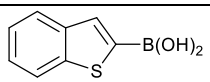
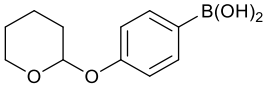
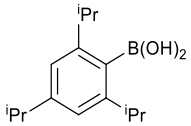


Table 5.2: Substrate Scope

Entry	Boronic acid	Catalyst	Time (mins)	Yield	**184**:**186**
1	 **163a**	Au(I) cat.	5	92%	18:1
		No cat.	**5**	**73%**	**>20:1**
2	 **163d**	Au(I) cat.	5	85%[a]	12:1
		No cat.	**5**	**77%**	**>20:1**
3	 **163u**	**Au(I) cat.**	**5**	**100%**	**>20:1**
		No cat.	5	77%	>20:1
4	 **163al**	**Au(I) cat.**	**5**	**100%[a]**	**>20:1**
		No cat.	5	62%[b]	>20:1
5	 **163w**	**Au(I) cat.**	**5**	**71%**	**>20:1**
		No cat.	5 60	33% 58%[c]	>20:1 >20:1
6	 **163h**	Au(I) cat.	5	69%	1.3:1[d]
		No cat.	5	60%	2.5:1[d]

7	 **163f**	**Au(I) cat.**	**5**	**78%**	**>20:1**
		No cat.	5	25%	>20:1
8	 **163l**	Au(I) cat.	5	Trace product	
		No cat.	5	No reaction	
9	 **163am**	**Au(I) cat.**	**5**	**62%**	**>20:1**
		No Cat.	5	13%	>20:1
10	 **163r**	**Au(I) cat.**	**10**	**78%[e]**	**>20:1**
		No cat.	10	10%	>20:1
			60	16%[c]	>20:1
11	 **163an**	Au(I) cat.	5	30%	1:1[f]
			15	31%	1:1[f]
		No cat.	15	9%	1:1[f]
12	 **163p**	Au(I) cat.	5	45%  **184p** +  **184p'**	
		No cat.	5	35%	>20:1
			30	42%	>20:1
13	 **163ao**	Au(I) cat.	5	No reaction	
			60	No reaction	
		No cat.	5	No reaction	
14	 **163ap**	Au(I) cat.	5	Complex mixture of products	
		No cat.	**5**	**100%**	**>20:1**

15	 163aq	Au(I) cat.	5	Complex mixture of products	
		No Cat.	**5**	**32%**	**>20:1**
16	 163ar	Au(I) cat.	5	Complex mixture of products	
		No cat.	5	Complex mixture of products	
17	 163ad	Au(I) cat.	5	Complex mixture of products	
		No cat.	**5**	**51%**	**>20:1**
18	 163ah	Au(I) cat.	5	Complex mixture of products	
		No cat.	-	-	
19	 163ae	Au(I) cat.	5	Complex mixture of products	
		No cat	**5**	**78%**	**>20:1**
20	 163ac	Au(I) cat.	5	22% Complex mixture of products	
		No cat.	**5**	**60%[h]**	**>20:1**
21	 163aa	**Au(I) cat.**	**3 h**	**78%[g]**	**>20:1**
		No cat.	3 h	14%[g]	>20:1

[a]Temperature increased to 100 °C. [b]Unidentified side product observed, which was inseperable from product.[c]Carried out by Conor Fletcher with 1.1 equiv. of NIS.[d]Iododeboronation *vs* protodeboronation. [e]Only 50% yield after 5 mins. [f]iododeboronation:homocoupling. [g]Carried out with 1.1 equiv. of NIS. [h]1 bead of 4 Å molecular sieves added.

Both the gold(I)-catalysed reactions and the uncatalysed reactions were investigated. This was carried out in order to determine whether the gold catalysed reaction had any advantages over the uncatalysed reaction or vice versa.

For strongly electron-donating boronic acids, entries 1-2, the catalysed reaction provides higher yielding reactions but poor selectivity for the *ipso*-iodinated product *vs* the overiodinated product (18:1 and 12:1 *vs* >20:1 for **163a** and **163d**, entries 1 and 2). With boronic acids which are less electron-rich (**163u** and **163al**), overiodination is not a competing side reaction. This is as expected, as electron-rich aryls are much more likely to undergo electrophilic aromatic substitution than their less electron-rich counterparts. With mildly electron-rich boronic acid **163al** the catalysed reaction is much more efficient (100% *vs* 62%, entry 4) and is cleaner (inseperable side product produced in the uncatalysed reaction). However, the presence of phenolic proton in **163h** causes both the catalysed and uncatalysed reaction to produce significant quantities of the protodeboronated side product **166h** (entry 6). For electron-rich boronic acids, the uncatalysed reaction is preferred, as although the yields are slightly lower, selectivity and cost effectiveness are better.

For electron-poor boronic acids the uncatalysed reaction produces poor yields of the desired products, even after extended reaction times. However, under Au(I)-catalysis the yields are significantly improved. For example, for boronic acids **163f**, **163am**, and **163r**, the uncatalysed reaction produced the iodinated product in less than 25% yields. Under gold(I)-catalysis, the yields were significantly improved to >62% in the same time period (between 5 and 10 mins, entries 7, 9 and 10). There are a few exceptions to this, including boronic acids containing a carboxylic acid moiety **163l** which only produces trace amounts of product (entry 8). Likewise, **163an** containing a fluorine substituent also reacted slowly under both sets of conditions and, in both cases, produced a significant quantity of the homocoupled product (entry 11). With an acetyl functionality (**163p**) the uncatalysed reaction, although slower than previous reactions, is preferred and gives 42% of the desired product after 30 mins (entry 12). Although the gold(I)-catalysed reaction is faster, it produces a 1:1 ratio of the desired iodinated product **184p** along with the undesired α-iodination product **184p'**.

Next, boronic acids with *N*-containing substituents were investigated. Boronic acid **163ao** containing an amide functionality was investigated (entry 13). No product was observed under either set of conditions and only starting material was recovered. This may be due to the coordination of the nitrogen lone pair to the Au(I) catalyst; effectively poisoning the active catalyst. However, it is unclear why the uncatalysed reaction does not proceed. Therefore boronic acids **163ap**-**163ar**, where the nitrogen lone pair is not

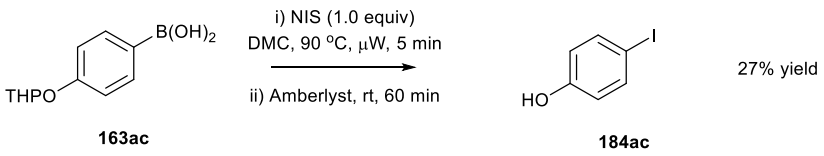
as coordinating as in the previous boronic acid **163ao**, was investigated. Under Au(I) catalysis, *N*-containing arylboronic acids tend to produce a complex mixture of products (entries 14-16). This may be due to overiodination as the aromatic rings are highly electron-rich. Pleasingly, when the uncatalysed reactions were performed the desired product **184ap** was produced in quantitative yields (entry 14). Boronic acid **163aq** containing a carbazole functionality also produced the desired iodinated product, albeit in moderate yields, 32% (entry 15).

Heterocyclic boronic acids (entries 17-19), followed the same trend as the N-containing arylboronic acids, with the uncatalysed reaction providing good to excellent yields for the desired iododeboronated products (entries 17 and 19). However, the addition of the Au(I)-catalyst provided a complex mixture of products (entries 17-19).

The reaction also works well for boronic acids containing acid-sensitive functional groups **163ac**. Whilst the gold-catalysed reaction resulted in a complex mixture of products, the presence of molecular sieves in the uncatalysed reaction provided good yields of the desired product **184ac** (60%, entry 20).

Finally, sterically hindered boronic acids **163aa** undergo iododeboronation effectively under Au(I)-catalysis. However, longer reaction times of 3 hours are needed for good conversions (entry 21). In contrast, the uncatalysed reaction is extremely slow, producing only 14% of **184aa** even after 3 hours.

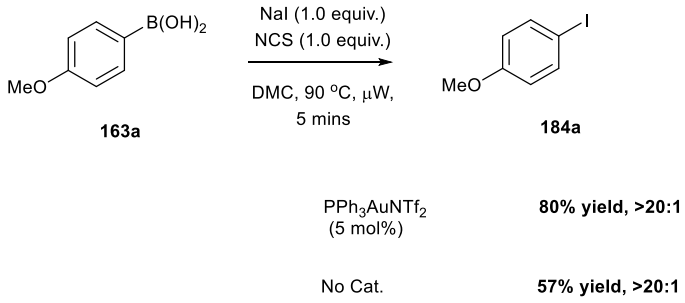
Since the presence of a phenolic proton seems to be a limitation for this reaction (Table 5.2, entry 6) it was speculated whether the THP protected phenol boronic acid **163ac** can be used, with addition of acidic resin amberlyst after the reaction with NIS to produce iodinated phenol **184ac** (Scheme 5.8). The THP group was indeed removed after stirring with amberlyst at room temperature for 1 h, however, only moderate yields of **184c** were obtained (Scheme 5.8). This approach was therefore only partially successful in overcoming the limitation.



163ac **184ac**

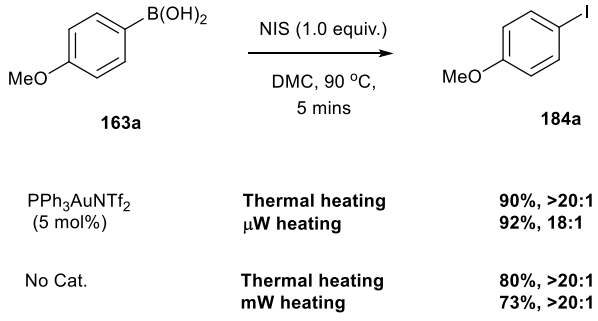
Scheme 5.8: Deprotection of THP boronic acid to form 4-iodophenol.

In order for this procedure to be adapted for radiolabelling, the reaction conditions must still give excellent yields when NIS is formed *in situ* from NCS and NaI. This is because radiolabelled NaI is commercially available where NIS is not. Therefore, boronic acid **163a** was added to a pre-mixed solution of NaI and NCS. Under Au(I)-catalysis, product **184a** was isolated in an excellent yield (80%), which is only slightly lower than when the commercially available NIS is used (92%) (Scheme 5.9). The reaction also gives moderate yields when no gold(I) catalyst is used, 57% (Scheme 5.9).



Scheme 5.9: Iododeboronation by forming NIS *in situ* from NaI and NCS. NaI and NCS were pre-mixed in DMC for 10 minutes prior to reaction.

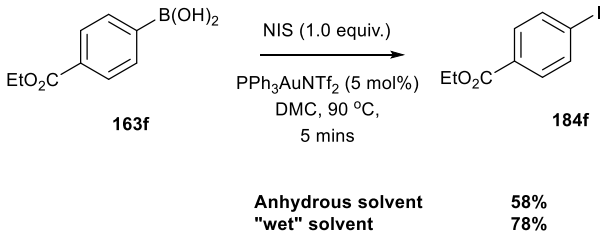
In order to establish whether the reaction could be carried out without the use of a microwave, the reaction was placed into a sealed tube and placed in an oil bath. Excellent yields were obtained with and without catalyst under thermal heating (Scheme 5.10). Both yields obtained by thermal heating were within error of the reactions which were carried out in the microwave.



Scheme 5.10: Thermal heating *vs* microwave heating.

It should be noted that the reaction is not particularly sensitive to air and moisture and therefore provides a very practical, fast and efficient procedure. In fact, wet solvent enhances the gold(I)-catalysed reactions as shown in Scheme 5.11. We have previously

shown that water aids the transmetallation between PPh_3AuNTf_2 and the aryl boronic acids (see page 159), which may explain the better yields in non-anhydrous solvent.



Scheme 5.11: Effects of anhydrous solvent on reaction yields.[1]

[1] Solvent was left open overnight before use.

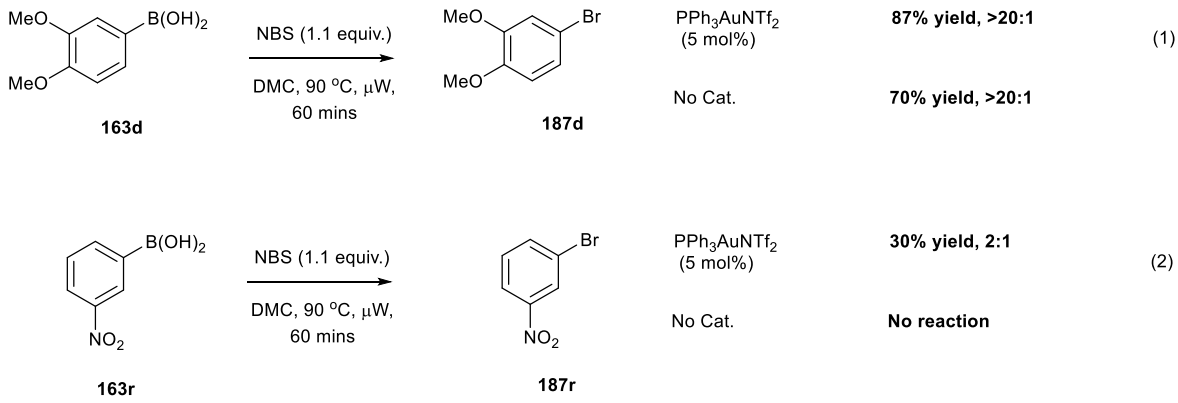
5.5 Conclusions

The use of NIS and dimethyl carbonate as a "green" solvent allowed for a quick and efficient iododeboronation reaction. The reaction is air and moisture stable and two complementary procedures have been developed: with and without Au(I)-catalysis. The gold(I)-catalysed reactions are preferred for electron-poor or sterically hindered arylboronic acids, where the uncatalysed reaction provided poor yields of the desired products. For electron-rich boronic acids, gold(I)-catalysis provided slightly better yields, although they were not significant enough to warrant the use of a catalyst. Heterocylic and *N*-containing boronic acids only work well in the uncatalysed reaction.

5.6 Future Work

Future work could potentially involve the use of different electrophilic sources such as NBS and NCS to obtain various halogenated aromatics.

Initial experiments were performed using NBS as a source of "Br^+" with electron-rich boronic acid **163d**. These results provided excellent yields of the desired products both with and without catalyst (Scheme 5.12, Eq. 1). However, upon adapting the procedure for electron-withdrawing boronic acids, low yields were obtained (Scheme 5.12, Eq. 2).



Scheme 5.12: Initial bromodeboronation results.

Since electron-withdrawing boronic acids provided only mixtures of the bromodeboronation product and protodeboronation product in poor yields, further optimisation is needed. Initial results for electron-donating boronic acids look promising.

5.7 Experimental

Chemical shifts (δ in ppm) were referenced to tetramethylsilane (TMS) or to residual solvent peaks. *J* values are given in Hz and s, bs, d, dd, ddd, dt, t, td, tt, q, qn, sext and m abbreviations correspond to singlet, broad singlet, doublet, doublet of doublet, doublet of doublet of doublets, doublet of triplets, triplet, triplet of doublets, triplet of triplets quartet, quintet, sextet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea. Infrared spectra were obtained deposited neat or as a chloroform solution to a diamond/ZnSe plate. All boronic acids were purchased and used without further purification unless otherwise stated. Dimethylcarbonate (DMC) was purchased and used without further purification. If poor yields were obtained, the dimethyl carbonate was left open to air for 24 - 48 h before use in order to make sure that the solvent was wet enough to aid transmetallation. CEM Microwave Discover was used for microwave heating, using sealed tubes and external surface sensor. The gold(I)-catalysed reactions were carried out without the need for dry solvents or inert atmosphere, unless stated otherwise.

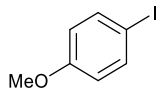
General procedure A: Gold(I)-catalysed reactions

Boronic acid **163** (0.10 mmol, 1.0 equiv.), NIS (0.10 mmol, 1.0 equiv.), PPh_3AuNTf_2 (3.7 mg, 5 mol%) and DMC (0.4 ml) were added to a microwave tube and heated under microwave irradiation at 90 ^{o}C for 5 minutes. The resulting solution was passed through a plug of silica and washed with 20:1 hexane/ether to yield product **184**. The crude product was purified by column chromatography as required.

General procedure B: No catalyst

Boronic acid **163** (0.10 mmol, 1.0 equiv.), NIS (0.10 mmol, 1.0 equiv.) and DMC (0.4 ml) were added to a microwave tube and heated under microwave irradiation at 90 ^{o}C for 5 minutes. The resulting solution was passed through a plug of silica and washed with 20:1 hexane/ether to yield product **184**. The crude product was purified by column chromatography as required.

1-Iodo-4-methoxybenzene (184a)[6]



General procedure A followed to yield a mixture of products **184a** and **186a** in a 18:1 ratio as a white solid (92%, 21.6 mg, 0.092 mmol).

General procedure B followed to yield product **184a** as a white solid (73%, 17.4 mg, 0.074 mmol).

Procedure for forming NIS *in situ*

A solution of NaI (15.3 mg, 0.102 mmol, 1.0 equiv) and NCS (13.2 mg, 0.099 mmol, 1.0 equiv.) in DMC (0.4 ml) was stirred at room temperature for 10 mins. Boronic acid **163a** (15.2 mg, 0.10 mmol, 1.0 equiv.) and PPh_3AuNTf_2 (3.7 mg, 5 mol%) was added to the reaction mixture and heated under microwave irradiation for 5 mins at 90 ^oC. The crude mixture was then passed through a plug of silica and washed with 20:1 hexane/ether to yield product **184a** as a white solid (80%, 19.4 mg, 0.08 mmol).

This procedure can also be carried out without the addition of PPh_3AuNTf_2 to yield product **184a** as a white solid (57%, 13.9 mg, 0.057 mmol).

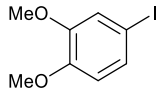
Procedure for thermal heating

Boronic acid **163a** (15.3 mg, 0.101 mmol, 1.0 equiv.), NIS (22.6 mg, 0.100 mmol, 1.0 equiv.), PPh_3AuNTf_2 (3.8 mg, 5 mol%) and DMC (0.4 ml) were added to a sealed tube and heated in a silicon oil bath at 90 ^oC for 5 mins. The crude mixture was then passed through a plug of silica and washed with 20:1 hexane/ether to yield product **184a** as a white solid (90%, 22.0 mg, 0.090 mmol).

This procedure can also be carried out without the addition of PPh_3AuNTf_2 to yield product **184a** as a white solid (73%, 19.2 mg, 0.073 mmol).

Mp: 56-58 ^oC ($CDCl_3$) [Lit.[11] mp 53-55 ^oC]; ν_{max} (cm^{-1}) 3065, 2962, 2937 (C-H), 1484, 1455, 1439 (Ar C-C), 1242 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (2H, d, J = 6.8 HZ, Ar-H), 6.68 (2H, d, J = 6.8 Hz, Ar-H), 3.78 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 159.6 (C), 138.3 (CH), 116.5 (CH), 82.8 (C), 55.5 (CH_3).

4-Iodo-1,2-diemethoxybenzene (184d)[12]

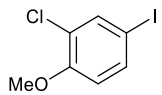


General procedure A followed but the reaction was carried out at 100 °C instead of 90 °C, to yield a mixture of products **184d** and **186d** in a 12:1 ratio as a yellow oil (85%, 22.5 mg, 0.085 mmol).

General procedure B followed but the reaction was carried out at 100 °C instead of 90 °C, to yield product **3a** as a yellow oil (70%, 18.4 mg, 0.070 mmol).

ν_{max} (cm^{-1}) 2944, 2947, 2848 (C-H), 1447, 1453, 1435 (Ar C-C), 1196 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (1H, dd, *J* = 8.4, 2.0 Hz, Ar-H), 7.12 (1H, d, *J* = 2.0 Hz, Ar-H), 6.62 (1H, d, *J* = 8.4 Hz, Ar-H), 3.85 (3H, s, OCH_3), 3.84 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.9 (C), 149.2 (C), 129.9 (CH), 120.5 (CH), 113.3 (CH), 82.4 (C), 56.2 (CH_3), 56.1 (CH_3).

2-Chloro-4-iodo-1-methoxybenzene (184u)[13]



General procedure A followed, to yield a mixture of products **184u** as a white solid (100%, 26.6 mg, 0.10 mmol).

General procedure B followed to yield product **184u** as a white solid (77%, 20.6 mg, 0.077 mmol).

Mp: 96-97 °C ($CDCl_3$) [Lit.[14] mp 93-95 °C]; ν_{max} (cm^{-1}) 3066, 2934, 2837 (C-H), 1476, 1460, 1437 (Ar C-C), 1250 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, *J* = 2.2 Hz, Ar-H), 7.51 (1H, dd, *J* = 8.7, 2.2 Hz, Ar-H), 6.68 (1H, d, *J* = 8.7 Hz, Ar-H), 3.88 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.2 (C), 138.3 (CH), 136.7 (CH), 123.9 (C), 114.1 (CH), 82.0 (C), 56.3 (CH_3).

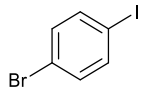
1-Iodo-2-methylbenzene (184al)[6]

General procedure A followed but the reaction was carried out at 100 °C instead of 90 °C, to yield product **184al** as a yellow oil (100%, 21.5 mg, 0.100 mmol).

General procedure B followed but the reaction was carried out at 100 °C instead of 90 °C, to yield product **184al** and an unidentified side product as a yellow oil (62%, 13.2 mg, 0.062 mmol).

ν_{max} (cm^{-1}) 3055, 2919 (C-H), 1473, 1462, 1453 (Ar C-C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (1H, d, *J* = 7.6 Hz, Ar-H), 7.23-7.25 (2H, m, Ar-H), 6.84-6.96 (1H, m, Ar-H) 2.44 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.5 (C), 139.1 (CH), 129.9 (CH), 128.3 (CH), 127.5 (CH), 101.3 (C), 28.3 (CH_3).

1-Bromo-4-iodobenzene (184w)[10]

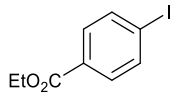


General procedure A followed to yield product **184w** as a white solid (71%, 20.0 mg, 0.071 mmol).

General procedure B followed to yield product **184w** as a white solid (33%, 9.2 mg, 0.033 mmol).

Mp: 94-96 °C ($CDCl_3$) [Lit.[15] mp 91-92 °C (ethanol)]; ν_{max} (cm^{-1}) 3071, 2923 (C-H), 1484, 1467, 1447 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.54 (2H, d, *J* = 8.6 Hz, Ar-H), 7.23 (2H, d, *J* = 8.6 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 139.2 (CH), 133.6 (CH), 122.3 (C), 92.2 (C).

Ethyl 4-iodobenzoate (184f)[12]

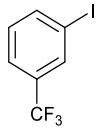


General procedure A followed to yield product **184f** as a colourless oil (78%, 21.4 mg, 0.078 mmol).

General procedure B followed to yield product **184f** as a colourless oil (25%, 7.0 mg, 0.025 mmol).

ν_{max} (cm^{-1}) 3069, 2976, 2934 (C-H), 1715 (C=O), 1476, 1463, 1444 (Ar C-C), 1266 (C-O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 8.8 Hz, Ar-H), 7.74 (2H, d, *J* = 8.8 Hz, Ar-H), 4.36 (2H, q, *J* = 7.1 Hz, $OC\underline{H}_2CH_3$), 1.39 (3H, t, *J* = 7.1 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.2 (C), 137.9 (CH), 131.1 (CH), 130.2 (C), 100.7 (C), 61.4 (CH_2), 14.4 (CH_3).

1-Iodo-3-(trifluoromethyl)benzene (184am)[16]

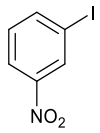


General procedure A followed to yield product **184am** as a brown oil (62%, 16.7 mg, 0.062 mmol).

General procedure B followed to yield product **184am** as a brown oil (13%, 3.4 mg, 0.013 mmol).

ν_{max} (cm^{-1}) 3070, 2975 (C-H), 1474, 1421 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, br s, Ar-H), 7.90 (1H, d, *J* = 7.9 Hz, Ar-H), 7.60 (1H, d, *J* = 8.6 Hz, Ar-H), 7.22 (1H, t, *J* = 7.9 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 141.0 (CH, q, *J* = 1.1 Hz), 134.4 (CH, q, *J* = 3.9 Hz), 132.8 (C, q, *J* = 32.8 Hz), 130.5 (CH), 124.6 (CH, q, *J* = 14.1 Hz), 121.3 (C, q, *J* = 273.2 Hz), 94.0 (C).

1-Iodo-3-nitrobenzene (184r)[5]

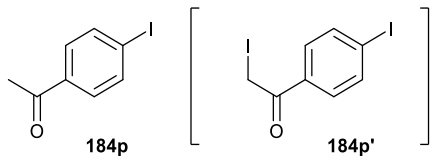


General procedure A followed but reaction time increased to 10 mins to yield product **184r** as a yellow oil (78%, 19.2 mg, 0.077 mmol).

General procedure B followed but reaction time increased to 60 mins using 1.1 equiv. of NIS to yield product **184r** as a yellow oil (16%, 4.0 mg, 0.016 mmol).

ν_{max} (cm^{-1}) 3088, 2858 (C-H), 1518, 1340 (NO_2), 1460, 1418 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (1H, t, *J* = 1.9 Hz, Ar-H), 8.21 (1H, ddd, *J* = 7.9, 1.9, 1.0 Hz), 8.03 (1H, ddd, *J* = 7.9, 1.9, 1.0 Hz), 7.26 (1H, t, *J* = 7.9 Hz); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 148.7 (C), 143.6 (CH), 132.6 (CH), 130.8 (CH), 122.9 (CH), 93.6 (C).

1-(4-iodophenyl)ethan-1-one (184p)[6]

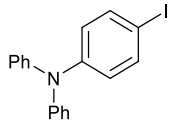


General procedure A followed to yield a 1:1 ratio of **184p** and **184p'** (45%, 10.9 mg, 0.045 mmol) as an inseparable mix.

General procedure B followed to yield product **184p** as white solid (35%, 8.6 mg, 0.035 mmol).

Mp: 86-87 °C ($CDCl_3$) [Lit.[17] mp 86-87 °C (benzene)]; ν_{max} (cm^{-1}) 2972 (C-H), 1667 (C=O) 1471, 1389 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (2H, d, *J* = 8.6 Hz, Ar-H), 7.66 (2H, d, *J* = 8.6 Hz, Ar-H), 2.57 (3H, s, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 197.5 (C), 138.0 (CH), 136.5 (C), 129.9 (CH), 101.2 (C), 26.6 (CH_3).

4-Iodo-*N*,*N*-diphenylaniline (184ap)[18]

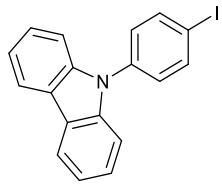


General procedure A followed to yield a complex mixture of products.

General procedure B followed to yield product **184ap** as a yellow oil (100%, 24.9 mg, 0.100 mmol).

ν_{max} (cm^{-1}) 3034 (C-H), 1481, 1311 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (2H, d, *J* = 8.9 Hz, Ar-H), 7.13-7.21 (4H, m, Ar-H), 6.92-7.02 (6H, m, Ar-H), 6.74 (2H, d, *J* = 8.9 Hz, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 147.9 (C), 147.4 (C), 138.2 (CH), 129.5 (CH), 125.4 (CH), 124.7 (CH), 123.5 (CH), 84.9 (C).

9-(4-Iodophenyl)-9*H*-carbazole (184aq)[19]

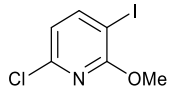


General procedure A followed to yield a complex mixture of products.

General procedure B followed to yield product **184aq** as an orange oil (32%, 11.8 mg, 0.032 mmol).

ν_{max} (cm^{-1}) 3058 (C-H), 1450, 1483, 1493 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (2H, dt, *J* = 7.7, 1.1 Hz, Ar-H), 7.93 (2H, d, *J* = 8.7 Hz, Ar-H), 7.26-7.45 (8H, m, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 140.5 (C), 139.2 (CH), 137.7 (C), 129.1 (CH), 126.2 (CH), 123.7 (C), 120.5 (CH), 120.4 (CH), 109.7 (CH), 92.2 (C).

6-Chloro-3-iodo-2-methoxypyridine (184ad)[20]

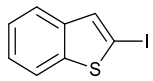


General procedure A followed to yield a complex mixture of products.

General procedure B followed to yield product **184ad** as a white solid (51%, 13.6 mg, 0.050 mmol).

Mp: 65-66 °C ($CDCl_3$); ν_{max} (cm^{-1}) 2951 (C-H), 1462, 1409, 1365 (Ar C-C), 1141 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (1H, d, *J* = 7.8 Hz, Ar-H), 6.70 (1H, d, *J* = 7.8 Hz, Ar-H), 3.99 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 161.9 (C), 149.8 (CH), 148.8 (C), 118.2 (CH), 76.8 (C), 55.5 (CH_3).

2-Iodobenzo[*b*]thiophene (184ae)[5]

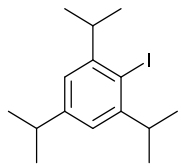


General procedure A followed to yield a complex mixture of products.

General procedure B followed to yield product **184ae** as a white solid (78%, 20.0 mg, 0.077 mmol).

Mp: 68-69 °C ($CDCl_3$) [Lit.[21] mp 63-65 °C (hexane)]; ν_{max} (cm^{-1}) 3053 (C-H), 1494, 1454, 1420 (Ar C-C), 1141 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.74-7.89 (1H, m, Ar-H), 7.68-7.73 (1H, m, Ar-H), 7.52-7.55 (1H, m, Ar-H), 7.27-7.31 (2H, m, Ar-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 144.5 (C), 140.9 (C), 133.9 (CH), 124.6 (CH), 124.5 (CH), 122.4 (CH), 121.4 (CH), 78.5 (C).

4-Iodo-1,3,4-triisopropylbenzene (184aa)[22]



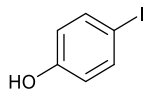
With gold catalyst: Boronic acid **163aa** (24.7 mg, 0.100 mmol, 1.0 equiv.), NIS (24.9 mg, 0.111 mmol, 1.1 equiv.), PPh_3AuNTf_2 (3.6 mg, 5 mol%) and DMC (0.4 ml) were added to the microwave tube and heated under microwave irradiation for 3 h at 90 °C.

The crude mixture was passed through a silica plug and washed with hexane to yield product **184aa** as a colourless oil (78%, 25.6 mg, 0.078 mmol).

Without gold catalyst: Boronic acid **163aa** (24.7 mg, 0.100 mmol, 1.0 equiv.), NIS (24.9 mg, 0.111 mmol, 1.1 equiv.) and DMC (0.4 ml) were added to the microwave tube and heated under microwave irradiation for 3 h at 90 ^{o}C. The crude mixture was passed through a silica plug and washed with hexane to yield product **184aa** as a colourless oil (14%, 4.6 mg, 0.014 mmol).

ν_{max} (cm^{-1}) 2958, 2926, 2868 (C-H), 1460, 1420, 1382 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.97 (2H, s, Ar-H), 3.41 (2H, sept, *J* = 6.9 Hz, $(CH_3)_2C\underline{H}CCI$), 2.89 (1H, sept, *J* = 6.9 Hz, $(CH_3)_2C\underline{H}C$), 1.27 (6H, d, *J* = 6.9 Hz, $(C\underline{H}_3)_2CHC$), 1.25 (12H, d, *J* = 6.9 Hz, $(C\underline{H}_3)_2CHCCI$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 150.9 (C), 149.0 (C), 122.2 (CH), 105.9 (C), 39.5 (CH), 34.0 (CH), 24.1 (CH_3), 23.6 (CH_3).

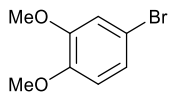
4-Iodophenol (184ae)[23]



General procedure B followed and once the reaction was complete, amberlyst (120 mg) was added to the solution and stirred for 60 mins at room temperature. The crude mixture was passed through a silica plug and washed with 20:1 hexane/ether then concentrated. The mixture was then purified by column chromatography (10:1 to 7:1 to 5:1 hexane/ether) to yield product **184ae** as a colourless oil (27%, 5.9 mg, 0.005 mmol).

ν_{max} (cm^{-1}) 3373 (O-H), 1484, 1580 (Ar C-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (2H, d, *J* = 8.9 Hz, Ar-H), 6.62 (2H, d, *J* = 8.9 Hz, Ar-H), 4.78 (1H, s, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 155.5 (C), 138.6 (CH), 117.9 (CH), 82.8 (C).

4-Bromo-1,2-dimethoxybenzene (187d)[24]



Gold(I)-catalysed reaction

Boronic acid **163d** (0.100 mmol, 1.0 equiv.), NBS (0.112 mmol, 1.1 equiv.), PPh_3AuNTf_2 (3.5 mg, 5 mol%) and DMC (0.4 ml) were added to a microwave tube and

heated under microwave irradiation at 90 °C for 60 minutes. The resulting solution was passed through a silica plug and washed with 20:1 hexane/ether to yield product **187d** as a yellow oil (87%, 18.9 mg, 0.087 mmol).

No catalyst

Boronic acid **163d** (0.085 mmol, 1.0 equiv.), NBS (0.112 mmol, 1.3 equiv.) and DMC (0.4 ml) were added to a microwave tube and heated under microwave irradiation at 90 °C for 60 minutes. The resulting solution was passed through a silica plug and washed with 20:1 hexane/ether to yield product **187d** as a yellow oil (70%, 12.9 mg, 0.059).

ν_{max} (cm^{-1}) 3000, 2932, 2836 (C-H), 1497, 1461, 1438 (Ar C-C), 1175 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.04 (1H, dd, *J* = 2.3, 8.5 Hz, Ar-H), 6.98 (1H, d, *J* = 2.3 Hz, Ar-H), 6.73 (1H, d, *J* = 8.5 Hz, Ar-H), 3.87 (3H, s, OCH_3), 3.85 (3H, s, OCH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 149.9 (C), 148.9 (C), 123.5 (CH), 114.9 (CH), 112.8 (C), 112.6 (CH), 56.22 (CH_3), 56.17 (CH_3).

5.8 References

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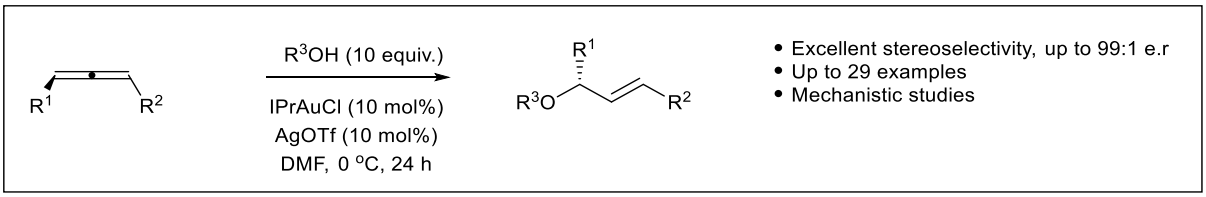
Chapter 6: Chirality Transfer in Hydroalkoxylation of 1,3-Disubstituted Allenes

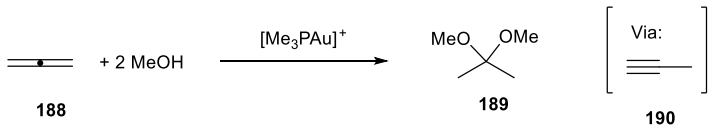


Acknowledgements

I would like to thank Daniel Sutherland (PhD Student) who collaborated on this project. Where work has been carried out by anyone other than the author, this has been explicitly stated.

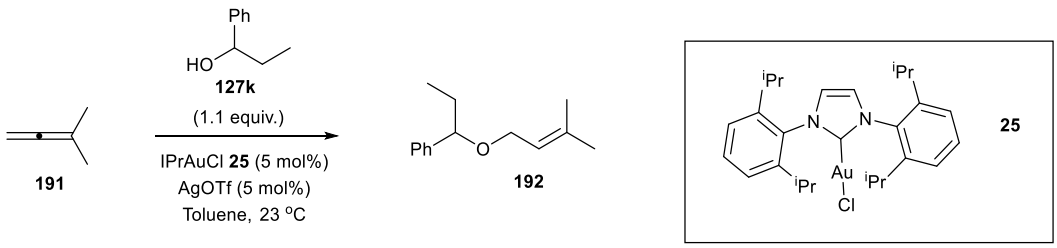
6.1 Introduction

Teles and co-workers first reported the hydroalkoxylation of allenes in the presence of a gold catalyst in 1998 when they discovered that cationic gold(I)-complexes were highly efficient catalysts for the addition of alcohols to alkynes.[1] The reaction involved reacting allene gas **188** with methanol to produce acetal **189** (Scheme 6.1). The formation of the acetal led Teles and co-workers to believe that the allene was isomerising to propyne **190**. This then reacted with two molecules of MeOH under gold(I)-catalysis in an alkyne hydroalkoxylation process to produce product **189**.[1]



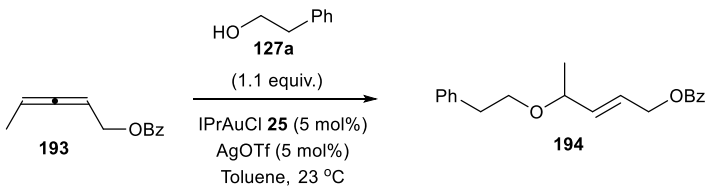
Scheme 6.1: First hydroalkoxylation reaction of allenes under Au(I) catalysis by Teles.

Since this discovery, much attention has been focused on the intramolecular hydroalkoxylation reaction of allenes, some of which has been discussed in Chapter 1. However, far fewer examples have been reported regarding the intermolecular hydroalkoxylation reaction. It was not until 2008 that Widenhoefer and co-workers reported the first gold(I)-catalysed regio- and stereoselective intermolecular hydroalkoxylation of allenes with alcohols to form allylic ethers (Scheme 6.2).[2]



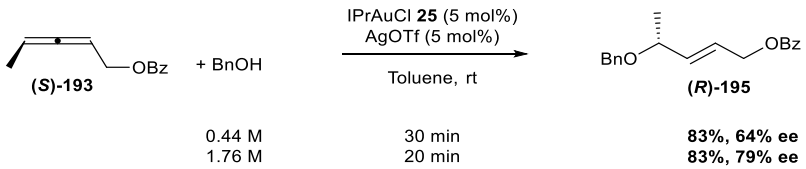
Scheme 6.2: Widenhoefer's intermolecular hydroalkoxylation of a 1,1-disubstituted allene.

Widenhoefer and co-workers found that this reaction was highly sensitive to the nature of the ligand and counterion, demonstrating that NHC complex **25** (Scheme 6.2) in combination with AgOTf was the most effective catalyst for the reaction. This reaction was effective with a wide range of substrates including monosubstituted, 1,1- and 1,3-disubstituted, trisubstituted and tetrasubstituted allenes. The alcohol nucleophile attacked at the least hindered end of the allene when the allenes were monosubstituted or 1,1-disubstituted. In the case of the 1,3-disubstituted allenes, the alcohol added to the more electron-rich methyl substituted allene terminus (Scheme 6.3).



Scheme 6.3: Widenhoefer's intermolecular hydroalkoxylation of a 1,3-disubstituted allene.

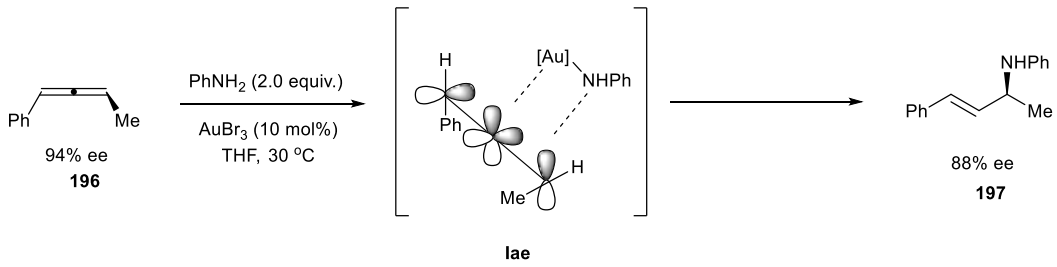
The group carried out a set of experiments to investigate chirality transfer with allene **193** containing an OBz substituent (Scheme 6.4). Widenhoefer and co-workers found that chirality transfer increased with increasing alcohol concentration (Scheme 6.4). This led them to believe that racemisation of the allene was occurring in an alcohol independent pathway.



Scheme 6.4: Widenhoefer's hydroalkoxylation reaction with chirality transfer.

They provided further evidence for this by treating allene **(*S*)-193** with gold(I) complex **25** and AgOTf in toluene at room temperature for 30 mins. These conditions led to complete racemisation of allene **(*S*)-193**. Chirality transfer was only investigated using one allene substrate **(*S*)-193** and %ee of the products **(*R*)-195** were modest at best.[2]

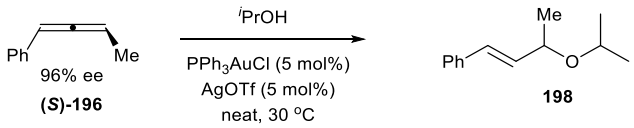
In 2009, Yamamoto and co-workers published studies on the hydrofunctionalization of allenes with both nitrogen and oxygen nucleophiles.[3] They initially began exploring the hydroamination of 1,3-disubstituted allenes and found that the reaction was only regioselective when allene **196** was used (Scheme 6.5). Furthermore, they found the enantioenriched allene **196** proceeded to form product **197** with good chirality transfer (Scheme 6.5).[3a]



Scheme 6.5: Originally proposed mechanism for Yamamoto's hydroamination of chiral allenes.

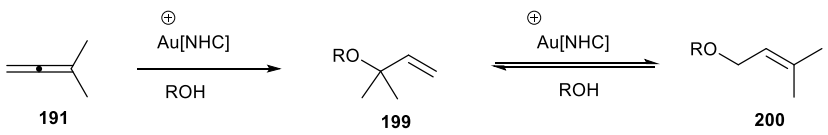
Yamamoto and co-workers suggest that the gold-amine complex forms first and approaches the least hindered end of the allene double bond as shown in **Iae** (Scheme 6.5). Their reasoning behind this is that if $AuBr_3$ had acted as a Lewis acid the opposite enantiomer would have been obtained, as aniline would have attacked the opposite face to the gold-coordination. Secondly, if a gold π-allyl complex had formed, the products would have been racemic. Finally, the formation of the gold-amine complex was strongly supported in that in the absence of the amine, a rapid racemisation of the allene is observed.[3a] However, later investigations by Toste *et al*. on the hydroamination of allenes have shown, through kinetic studies, that the reaction cannot be proceeding through an inner sphere mechanism and must be proceeding *via* the outer sphere pathway.[4]

Next Yamamoto and co-workers examined alcohol nucleophiles. Only allene **196** gave good regioselectivity. However, when they used enantioenriched allene **(*S*)-196** the products were racemic, suggesting that the addition of alcohol might occur after racemisation of the allene by the gold catalyst (scheme 6.6).[3a]



Scheme 6.6: Yamamoto's hydroalkoxylation of chiral allenes.

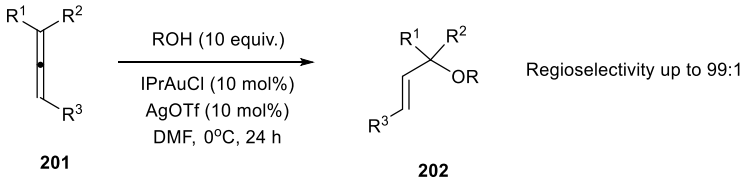
Following these reports, Paton and Maseras investigated the regioselectivity of the hydroalkoxylation reactions of 1,1-disubstituted allenes **191** using DFT (Scheme 6.7). They suggest that the regioselectivity observed by Widenhoefer and Yamamoto is due to the isomerisation of the kinetic product **199** to the thermodynamic product **200** rather than the nucleophile attacking at the least hindered terminus of the allene (Scheme 6.7).[5]



Scheme 6.7: Isomerisation of the kinetic allylic ether to the thermodynamic product.

In 2010, Lee and co-workers were able to isolate the tertiary allylic ether **202** by suppressing the isomerisation of the kinetic product.[6] The group found that the solvent and concentration of the alcohol were essential in preventing the isomerisation. The only solvent which produced excellent regioselectivity was DMF and an excess of 10

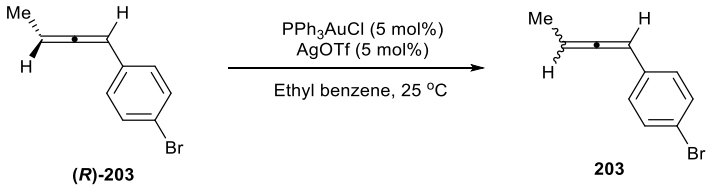
equivalents of alcohol was also required (Scheme 6.8).[6] It is thought that the use of DMF reduces the activity of the cationic catalyst IPrAu$^+$, possibly by reversible co-ordination.[7]



Scheme 6.8: Optimised conditions for the suppression of isomerisation of the kinetic product.

Both Widenhoefer and Yamamoto observed racemisation of the allene in the absence of a nucleophile under Au(I)-catalysis. In order to understand these results experimentally, Widenhoefer and co-workers studied the kinetics of the racemisation of axially chiral 1,3-disubstituted aryl allenes catalysed by gold(I)-complexes.[8]

Widenhoefer and co-workers initially began their investigations with enantioenriched allene **(*R*)-203** and subjected it to a catalytic mixture of 1:1 PPh_3AuCl and AgOTf in ethylbenzene at 25 °C, monitoring the enantiomeric excess over time (Scheme 6.9).

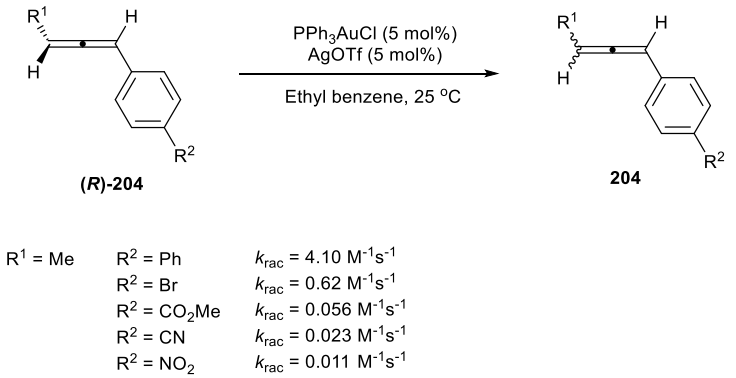


Scheme 6.9: Racemisation of **(*R*)-203** catalysed by a 1:1 mixture of PPh_3AuCl and AgOTf.

The group observed that there was a first-order dependence of the rate on **(*R*)-203** and calculated the rate constant k_{obs} for the racemisation of **203**. Neither PPh_3AuCl nor AgOTf alone catalysed the racemisation of **203**. This suggests that the active catalyst is indeed PPh_3AuOTf. By using this information they were able to determine the rate dependence of allene racemisation on the catalyst concentration. They found that there was a first order dependence on the rate of catalyst concentration and that the overall rate law for the gold catalysed racemisation was second order: rate = k_{rac}[***(R)*-203**][PPh_3AuOTf].[8]

The group then investigated the effect of allene electron density on the rate of gold catalysed racemisation. By changing the R^2 group of allene **204**, they found that the more

electron-withdrawing the substituent, the slower the racemisation of the allene (Scheme 6.10).



Scheme 6.10: The effect of allene electron density on the racemisation of the allene.

Widenhoefer and co-workers then investigated the effects of the electron-donor ability of the gold phosphine ligand on the racemisation of an allene. They observed that the rate constant for the racemisation increased three orders of magnitude when the electron donating ability of the phosphine decreased **205a-205d** (Figure 6.1).

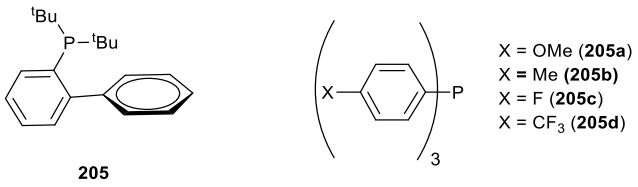
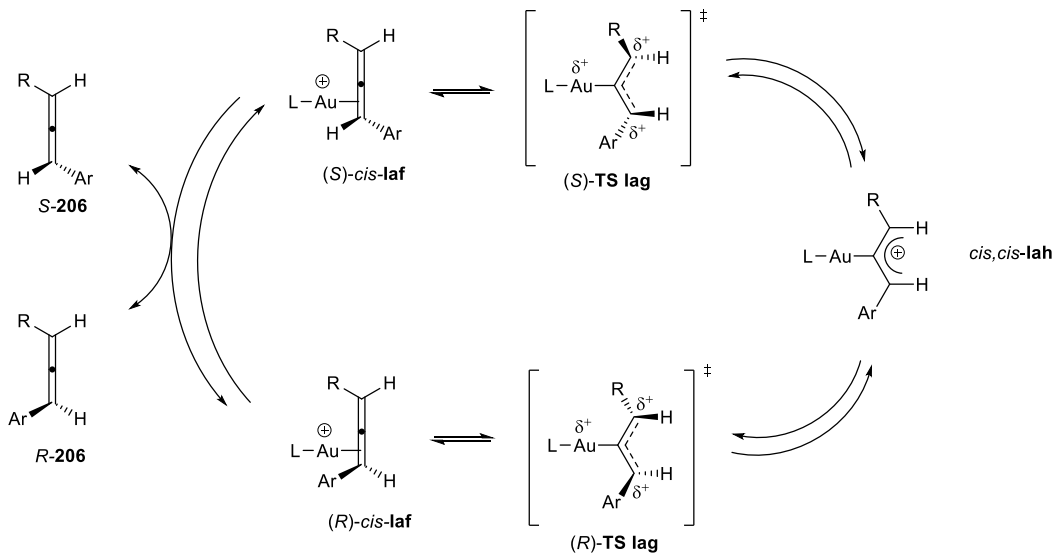


Figure 6.1: Phosphine ligands.

Several experiments were performed to study the counterion and solvent effects on racemisation. The results suggest that the counterion has little impact on the rate of racemisation. In contrast, there was a significant effect on the rate when the solvent polarity was increased. By changing the solvent from ethyl benzene to toluene, the rate constant for the racemisation of **204** differed by less than a factor of two. However, by changing the solvent to chlorobenzene or 1,2-dichloroethane the rates were $\geq$36- and $\geq$50-times faster, respectively, than the racemisation of **204** in toluene.[8]

Widenhoefer and co-workers propose that the racemisation of axially chiral allenes involves a rapid and reversible interconversion of the enantio-, diastereo-, and regioisomeric gold η^2-allene complexes **Iaf**. This is followed by turnover-limiting conversion of *cis*-**Iaf** to the achiral η^1-allylic cation intermediate *cis,cis*-**Iah** *via* the bent and twisted η^1-allene transition state *cis,cis*-**Iag** (Scheme 6.11).[8]



Scheme 6.11: Widehoefer's proposed mechanism for the gold-catalysed racemisation of aromatic allenes.

The reasoning behind this proposed mechanism was that the energy barriers for catalytic racemisation are much higher than the energy barriers for the inter- or intramolecular π-face exchange.[9] Therefore, they propose the reaction proceeds through an achiral η^1-allylic cation shown in Scheme 6.11.[8]

In summary, there are many examples of intramolecular hydroalkoxylations of allenes in the literature. However, there are far fewer examples of intermolecular hydroalkoxylations. Widenhoefer and co-workers successfully demonstrated the nucleophilic addition of alcohols to a variety of allenes including 1,3-disubstituted. In these cases, it is thought that the alcohol attacks at the more electron-rich terminus of the allene. They were able to demonstrate one example of chirality transfer and, through control studies, they propose that chirality transfer is dependant on the alcohol concentration. In the absence of a nucleophile the allene racemises under Au(I)-catalysis. Yamamoto and co-workers were also able to carry out intermolecular hydroalkoxylation reactions of 1,3-disubstituted allenes but observed regioselectivity issues in all but one substrate. Although the reaction proceeded with good chirality transfer with amine nucleophiles, the reaction was racemic with alcohols. By studying the kinetics on the racemisation of allenes under Au(I) catalysis, Widenhoefer and co-workers suggest that the electron density of the allene, the type of catalyst and the solvent polarity play an important role in the rate of racemisation of allenes.

6.2 Project Aims

Widenhoefer and Yamamoto have both shown that in the hydroalkoxylation of allenes, rapid racemisation of allenes occurs, resulting in either racemic products or an erosion of ee. The substrate scope of the reaction is also not known. This problem has remained unresolved and is a clear limitation in this area.

Meanwhile, the Lee group have recently demonstrated that gold(I)-catalysed allylic etherification reactions proceed with excellent chirality transfer if molecular sieves are included in the reaction (Chapter 2, Section 2.1).[10] Therefore, at the outset of this project, we proceeded to investigate whether a similar approach would allow us to develop an efficient hydroalkoxylation reaction of 1,3-disubstituted allenes that would proceed with good chirality transfer.

Scheme 6.12: Project aim.

If the addition of molecular sieves does not help the chirality transfer, our second option would be to investigate the DMF conditions which were successful for retarding further isomerisation in previous work (see Scheme 6.8).

6.3 Results and Discussion

6.3.1 Optimisation

The results obtained by Widenhoefer *et al.* originally showed an 83% yield of **(*R*)-195** in a 89.5:10.5 e.r (Table 6.1, entry 1). Upon repetition of Widenhoefer's conditions with allene **(*S*)-193**, the allylic ether **(*R*)-195** was obtained in an improved yield and e.r (95% and 93:7, entry 2). The reaction was then repeated but the Au(I)-catalyst was changed from IPrAuCl/AgOTf to PPh_3AuNTf_2 to avoid complications that could arise with excess silver salt (entry 3).[11] The change in catalyst resulted in longer reaction times but still produced an excellent yield of product **(*R*)-195** with a 92:8 e.r (entry 3). Therefore, subsequent reactions were carried out using PPh_3AuNTf_2.

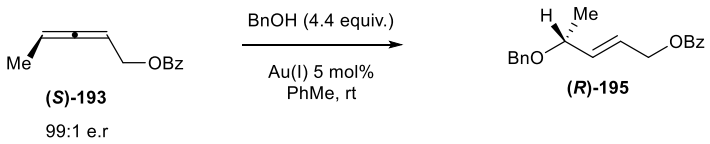


Table 6.1: Initial investigations.

Entry	Catalyst	Time	%yield	e.r
1[a]	IPrAucl/AgOTf	20 min	83%	89.5:10.5
2	IPrAuCl/AgOTf	20 min	95%	93:7
3	PPh_3AuNTf_2	4 h	95%	92:8

[a]Widenhoefer's original result.

Since the Lee group have demonstrated that molecular sieves improve the chirality transfer in the gold(I)-catalysed direct allylic etherification reaction, our initial studies began by adding 4 Å molecular sieves under Widenhoefers reaction conditions to study the effect that they would have on the chirality transfer (Table 6.2).

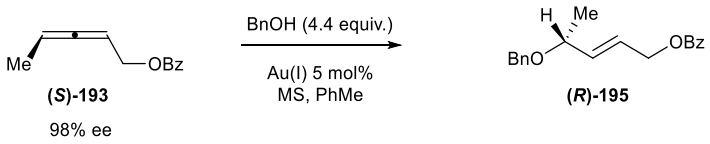


Table 6.2: Varying the mass of molecular sieves (4 Å) in the reaction.

Entry	Catalyst	Time	Temp	MS	%yield	e.r
1	PPh_3AuNTf_2 (2 x 5 mol%) 4 + 20 h	4 h + 20 h	rt	9 mg	Mainly SM	-
2	PPh_3AuNTf_2 (2 x 5 mol%) 7+17 h	24 h	rt	4 mg	30%	97:3
3	PPh_3AuNTf_2	4 + 1 h	rt + 60 °C	1 mg	43%	95:5
4	IPrAuCl/AgOTf	24 h	rt	7 mg	Mainly SM	-

Initially, 9 mg of molecular sieves were added to the reaction mixture. After 4 h only trace amounts of product were observed and a second portion of Au(I) was added and left for a further 20 h (Table 6.2, entry 1). No improvement in conversion was observed and therefore the mass of molecular sieves was reduced to 4 mg (entry 2). This resulted in a 30% yield of product **(*R*)-195** with a 97:3 e.r. This result demonstrates the e.r improves upon adding molecular sieves compared to the original result under Widenhoefers conditions (97:3 *vs* 93:7 e.r) but prevents the reaction from proceeding to full conversion. The mass of molecular sieves was further reduced to 1 mg (entry 3). Although a slight increase in yield was observed, the e.r of product **(*R*)-195** has decreased to 95:5. Finally, IPrAuCl/AgOTf was used instead of the Gagosz catalyst but once again only trace product was observed. For subsequent reactions 4 mg of molecular sieves were added to the reaction mixture.

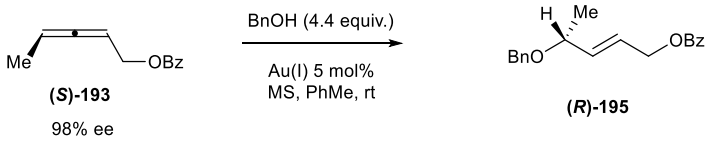


Table 6.3: Portionwise addition of Au(I) catalyst every 30 minutes.

Entry	Catalyst	Time	yield	e.r
1	PPh_3AuNTf_2 (5 mol%)	24 h	30%	97:3
2	PPh_3AuNTf_2 (4 x 5 mol%)	4.5 h	35%	95:5

In order to push the reaction to full conversion and increase the yield of product **(*R*)-195**, 4 portions of Au(I) were added to the reaction mixture every 30 minutes (Table 6.3, entry 2). Only a slight improvement of yield was observed (35% *vs*. 30%).

The equivalents of alcohol was then reduced from 4.4 to 1.1 equivalents but after 20 h only trace amounts of product **(*R*)-195** was observed (Table 6.4, entry 1). Next, 10 equiv. of alcohol was added and, although this reaction progressed a lot slower than previous reactions, a slight increase in chirality transfer was observed with a 98:2 e.r (entry 3). However, after 4 days only a 17% yield was observed. Therefore, in subsequent reactions 4.4 equivalents of alcohol was used.

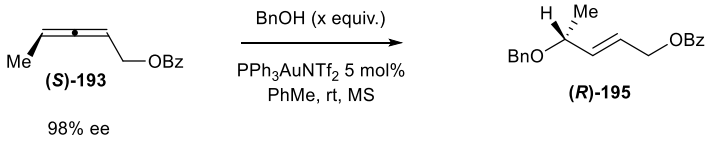


Table 6.4: Alcohol equivalents.

Entry	Equiv. of BnOH	Time	yield	e.r
1	1.1	20 h	Mainly SM	-
2	4.4	24 h	30%	97:3
3	10	4 days	17%	98:2

In a further attempt to push the reaction to full conversion, the temperature of the reaction was increased from rt to 50 °C (Table 6.5, entry 2). Although a slight improvement in yield was observed, the e.r of the product was reduced to 92:8.

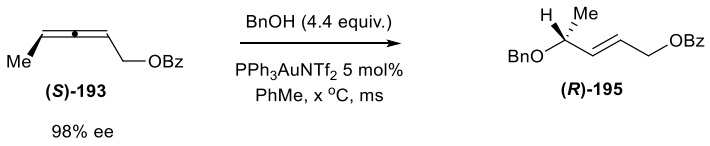


Table 6.5: Increase in temperature of the reaction.

Entry	Temperature	Time	yield	e.r
1	rt	24 h	30%	97:3
2	50	4 h	38%	92:8

In a final attempt to increase the yield of the reaction whilst maintaining a good chirality transfer, different additives were included in the reaction mixture (Table 6.6).

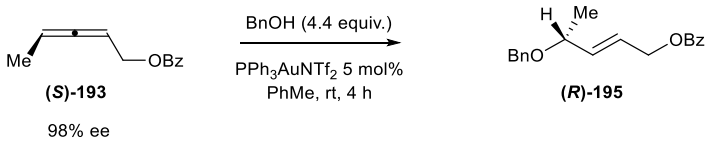


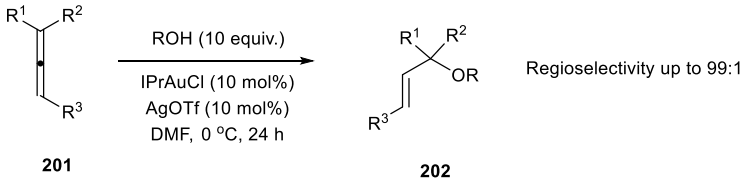
Table 6.6: Additives.

Entry	Time	Additive	Yield	e.r
1	20 h	4 mg of 4 Å MS + 1 equiv. of water	Mainly SM	-
2	4 days	4 mg of activated 4 Å MS	7%	98:2
3	4 h	4 mg of 4 Å MS (fine powder)	Only SM	-
4	4 h	4 mg of 4 Å MS (beads crushed into powder)	26%	97:3
5	4 h	4 mg of 5 Å MS (beads crushed into powder)	60%	83:17
6	4 h	4 mg of 5 Å MS (beads crushed into powder)	61%	95:5
7	4 h	4 mg of silica	50%	94:6
8	4 h	4 mg of neutral alumina	28%	97.5:2.5
9	4 h	2 mg of neutral alumina	58%	96:4
10	4 h	4 mg of basic alumina	41%	96:4
11	4 h	4 mg of acidic alumina	48%	97:3
12	4 h	1-5 mol% $Ga(OTf)_3$	34%	96

In order to prove the molecular sieves were not inhibiting the reaction by removing water, 1 equiv. of water was added to the reaction mixture (Table 6.6, entry 1). After leaving the reaction overnight it can be concluded that the addition of water slowed down the reaction. Since water appeared to slow down the reaction, activated molecular sieves were next attempted (entry 2). After 4 days only a 7% yield of product **(*R*)-195** was obtained but maintained a good e.r of 98:2. It was thought that the surface area of the molecular sieves may be having an effect on the reaction and this was investigated next (entries 3 and 4). By using finely powdered molecular sieves purchased from Aldrich in the reaction, only starting material was present after 4 h (entry 3). Next, molecular sieves in bead form were crushed using a mortar and pestle (entry 4). By decreasing the surface area, a 26% yield of product **(*R*)-195** was observed with a 97:3 e.r (entry 4). Next an increase in pore size was investigated by increasing the pore size from 4 Å to 5 Å. This resulted in an increased yield to 60% but a decrease in chirality transfer with an 83:17 e.r (entry 5). The crushing of molecular sieves by mortar and pestle proved to be unreliable, as, when attempts were made to repeat this experiment, different results were obtained (entry 6). The components which make up molecular sieves, silica and alumina, were then investigated as one of these components could be inhibiting the reaction (entries 7-11). The use of silica in the reaction increased the yield of product **(*R*)-195** to 50% with

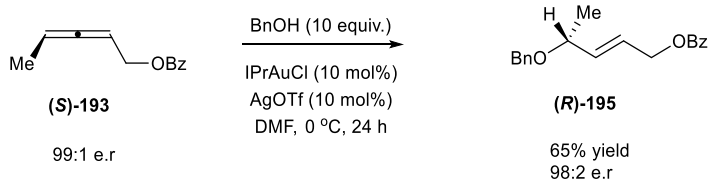
an e.r of 94:6 (entry 7). Next, neutral alumina was added to the reaction. This additive produced a 28% yield of product **(*R*)-195** with a 97.5:2.5 e.r (entry 8). This result is similar to the reactions containing molecular sieves and therefore, neutral alumina could potentially be inhibiting the reaction. Basic and acidic alumina were then investigated (entries 10-11). The use of acidic alumina produced product **(*R*)-195** in a slightly better yield than basic alumina, 48% *vs* 41% respectively, with the chirality transfer proving to be efficient in both reactions. Since the additives were only producing product **(*R*)-195** in poor to moderate yields, a different set of conditions were investigated next.

As discussed in section 6.1 the Lee group have previously worked on hydroalkoxylations of 1,1-disubstituted and 1,1,3-trisubstituted allenes (**201**). They found that the use of DMF with a large excess of alcohol resulted in a regioselective reaction by preventing the isomerisation of kinetic tertiary allylic ether product **202** to the thermodynamic primary allylic ether product (Scheme 6.13).[6]



Scheme 6.13: Lee group conditions for the hydroalkoxylations of allenes.

Since the addition of molecular sieves gave good e.r but poor conversion, we decided to investigate these conditions using allene **(*S*)-193** in the hope that these conditions could similarly improve the selectivity in this case. This resulted in an improved 65% yield of product **(*R*)-195** with an excellent 98:2 e.r (Scheme 6.14).

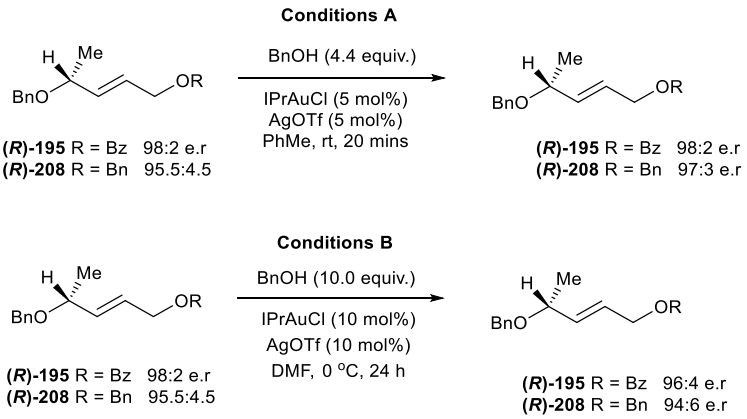


Scheme 6.14: Lee group allene conditions with allene **(*S*)-193**.

Since these conditions provided excellent enantiomeric ratios with decent yields, they were taken forward to investigate control reactions, substrate and nucleophile scopes.

6.3.2 Control reactions

Before proceeding with the substrate scope, control reactions were carried out in order to determine whether the racemisation of allene substrate **(*S*)-193** or the allylic ether product **(*R*)-195** was responsible for the erosion of the enantiomeric excess. In order to investigate this, allylic ether products **(*R*)-195** and **(*R*)-208** were resubjected under two sets of conditions. The original conditions used by Widenhoefer (Conditions A, Scheme 6.15) and our DMF conditions shown in Scheme 6.13 (Conditions B, Scheme 6.15).



Scheme 6.15: Resubjection of allylic ether products **(*R*)-195** and **(*R*)-208** to conditions A and B.

As shown in Scheme 6.15, allylic ether products **(*R*)-195** and **(*R*)-208** do not racemise under either set of conditions and cannot be the major cause of the erosion of enantiomeric excess.

Next, the starting material allene **(*S*)-193** was resubjected under both conditions A and B, with the addition of *tert*-butanol which is a poor nucleophile under these conditions. This allowed the reaction conditions to be replicated without hydroalkoxylation occurring, in order to study the allene racemisation under the reaction conditions (Table 6.7).

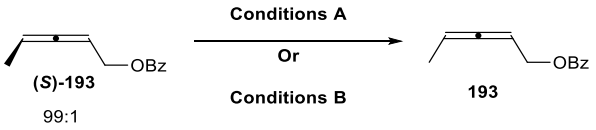


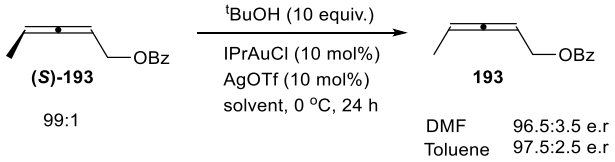
Table 6.7: Control reaction – allenes resubjected to reactions conditions

Entry	Time	Conditions A	Conditions B
1	20 min	98:2 e.r	98.5:1.5 e.r
2	2 h	89:11 e.r	96.5:3.5 e.r
3	24 h	Racemic	No allene remaining

Under both conditions A and B, after 20 minutes, no allene racemisation was observed (Table 6.7, entry 1). However, after 2 hours, conditions A resulted in a much faster racemisation than conditions B (entry 2). This suggests that the erosion of enantiomeric excess under Widenhoefer's conditions A is as a result of allene racemisation, but conditions B results in much slower allene racemisation.

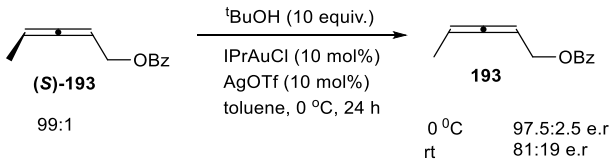
Investigations were then carried out to determine whether the solvent (toluene or DMF), temperature (0 °C or rt), or alcohol concentration is causing the difference in the rate of allene racemisation between conditions A and B.

Firstly, a racemisation control was carried out under conditions B but using toluene as the solvent instead of DMF (Scheme 6.16). With DMF as the solvent a 96.5:3.5 e.r was obtained. When the solvent was switched to toluene, the e.r was within error, 97.5:2.5. This suggests that the solvent difference between conditions A and B is not the most crucial factor for allene **(*S*)-193**.



Scheme 6.16: Effect of solvent on the racemisation of allene **(*S*)-193**.

The difference in temperature between conditions A and B, however, is significant and has a large impact on the enantiomeric ratio (Scheme 6.17). By performing the reaction at room temperature, rather than 0 °C, the e.r drops to 81:19.



Scheme 6.17: Effect of temperature on the racemisation of allene **(*S*)-193**.

The effect of solvent was then studied in the actual gold(I)-catalysed hydroalkoxylation reaction with allene **(*S*)-193** (Table 6.8).

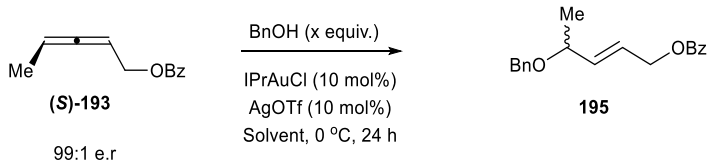
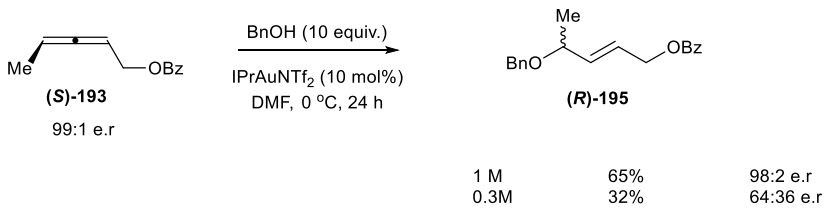


Table 6.8: Effect of solvent and alcohol concentration on the hydroalkoxylation of **(*S*)-193**.

Entry	Solvent	BnOH equiv.	e.r[a]	Yield (%)
1	DMF	10	98:2	65
2	Toluene	10	97:3	81
3	Toluene	4	97:3	85
4	**Toluene**	**2**	**96:4**	**78**
5	Toluene	1.1	93:7	74

[a] Determined by CSP-HPLC.

Once again the change of solvent from DMF to toluene had little effect on the enantiomeric ratio (98:2 *vs* 97:3), however, the yield was improved (65% *vs* 81%, entries 1 and 2). Alcohol concentration was then investigated (entries 3-5). The chirality transfer decreases slightly with decreasing alcohol concentration. Using 10 equiv. of BnOH resulted in a 97:3 e.r with an 85% yield of product **(*R*)-195** (entry 2). On decreasing the alcohol concentration to 1.1 equiv. a slight decrease in e.r to 93:7 with a 74% yield of product **(*R*)-195** was observed (entry 5). Therefore, we proceeded with the conditions shown in entry 4 (hereafter referred to as Conditions C) as the optimised conditions for the reaction. Conditions C provided a good compromise between lower alcohol equivalents and good e.r/yields. It should also be noted that upon decreasing the concentration of the reaction from 1 M to 0.3 M, a loss in chirality transfer is observed (64:36 e.r, Scheme 6.18).



Scheme 6.18: Decreasing concentration from 1 M to 0.3 M

To our surprise, when the substrate scope was carried out, conditions C only gave good yields specifically for allene **(*S*)-193** and it was discovered that conditions B outperformed the others in terms of chirality transfer. For example, when allene **(*S*)-209** with an OBn substituent is used instead of OBz in **(*S*)-193**, conditions B (95:5 e.r) outperform both A (81.19 e.r) and C (87:13 e.r) (Table 6.9, entries 1-3).

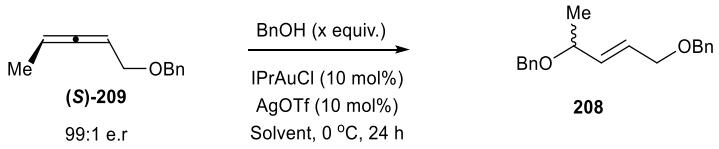


Table 6.9: Effect of solvent and alcohol concentration on allene **(*S*)-209**.

Entry	Solvent	Equiv. BnOH	Temperature (°C)	Conditions	e.r[a]	Yield (%)
1	Toluene	4.4	rt	Conditions A	81:19	37
2	**DMF**	**10**	**0**	**Conditions B**	**95:5**	**45**
3	Toluene	2	0	Conditions C	87:13	61
4	Toluene	10	0		92.5:7.5	65

[a]Determined by CSP-HPLC.

In this case, the switch from DMF to toluene produces a decreased e.r (entry 4). Therefore, we can conclude that solvent, temperature, and alcohol concentration all cumulatively effect the chirality transfer when comparing our conditions B to previously reported conditions A. Although the yield was low when using conditions B for substrate **(*S*)-193**, all other substrates produced good to excellent yields under conditions B (Table 6.10).

6.3.2 Substrate Scope

General conditions B were then used to investigate the allene substrate scope (Table 6.10). Our initial thoughts were that the OBz group plays an important role in the regioselectivity and the chirality transfer of the reaction. Therefore, different protecting groups on the oxygen were initially investigated.

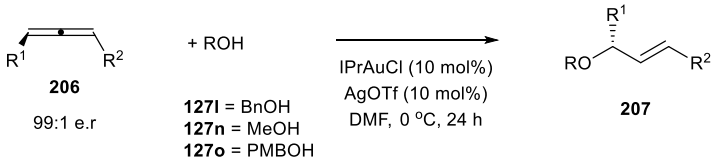
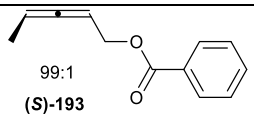
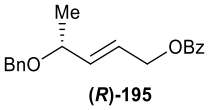
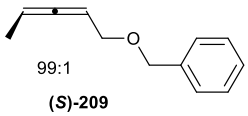
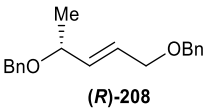
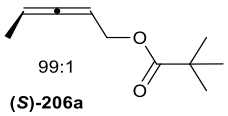
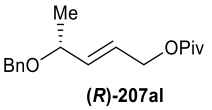
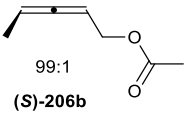
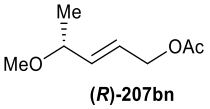
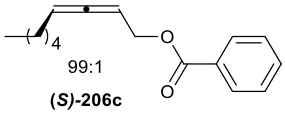
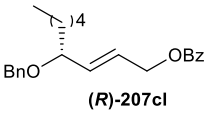
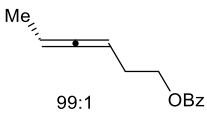
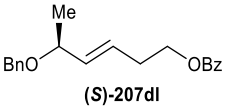
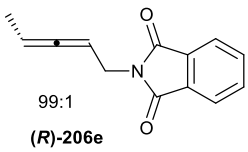
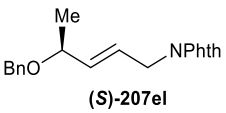
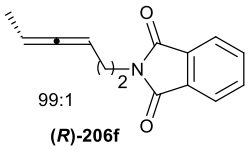
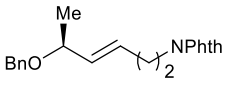
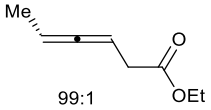
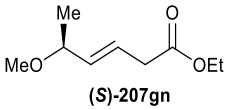
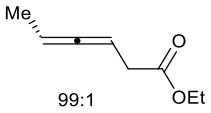
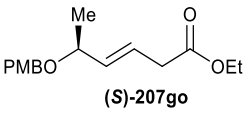
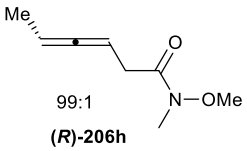
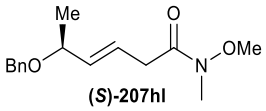
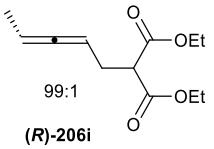
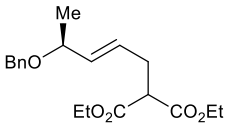
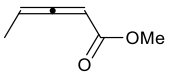
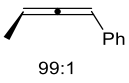
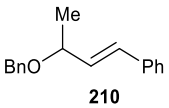
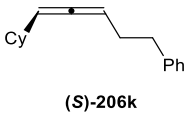
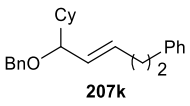
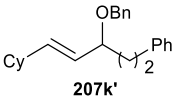
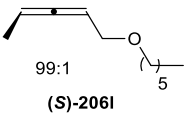
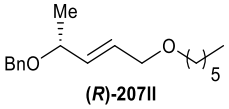


Table 6.10: Substrate scope

Entry	Allene	Product	Result[a]
1	 99:1 (*S*)-193	 (*R*)-195	65% 98:2 e.r[b]
2	 99:1 (*S*)-209	 (*R*)-208	45% 95:5 e.r[b]
3	 99:1 (*S*)-206a	 (*R*)-207al	70% 93:7 e.r[c]
4	 99:1 (*S*)-206b	 (*R*)-207bn	78% 94:6 e.r[c]
5	 99:1 (*S*)-206c	 (*R*)-207cl	91% 97:3 e.r[b]
6*	 99:1 (*R*)-206d	 (*S*)-207dl	79% 90:10 e.r[b]
7*	 99:1 (*R*)-206e	 (*S*)-207el	81% 97:3 e.r[b]

8*	 (*R*)-206f	 (*S*)-207fl	94% 81:19 e.r[b] 9:1 regioselectivity
9*	 (*R*)-206g	 (*S*)-207gn	92% 97:3 e.r[b]
10*	 (*R*)-206g	 (*S*)-207go	71% 95:5 e.r[b]
11*	 (*R*)-206h	 (*S*)-207hl	58% 91:9 e.r[b]
12*	 (*R*)-206i	 (*S*)-207il	86% 90:10 e.r[b]
13	 206j		Mainly **x** and complex mixture of products
14*	 (*S*)-196	 210	79%[d] Racemic 10:1 regioselectivity
15	 (*S*)-206k	 207k  207k'	71%[d] 1:0.7 regioselectivity
16	 (*S*)-206l	 (*R*)-207ll	94% 87:13 e.r[e]

[*]Carried out by Daniel Sutherland. [a]Isolated yields, >20:1 *E/Z* and regioselectivity by ^{1}H NMR analysis unless otherwise stated. MeOH **127n** was used when the product using BnOH **127l** is not seperable by CSP-HPLC, CSP-GC or chiral shift reagents. [b]Determined by CSP-HPLC. [c]Determined by ^{1}H NMR using chiral shift reagent (*R*)-(-)-1-(9-Anthryl)-2,2,2-trifluorethanol. [d]Combined yield [e]Determined by CSP-GC.

The removal of the carbonyl (entry 2, **(*S*)-209**) or the Ph (entries 3-4, **(*S*)-206a-b**) does not significantly affect the enantiomeric ratios and a high degree of chirality transfer, >94:6 e.r, occurs in all cases in moderate to good yields, 45-78%. The Me group was then replaced with an ^{n}pentyl chain resulting in good yield of product **(*R*)-207cl** with an excellent enantiomeric ratio, 97:3 e.r (entry 5). Next, an extra CH_2 group was inserted to move the OBz group further away from the allene **(*R*)-206d**. Although product **(*S*)-207dl** is still formed in an excellent yield, 79%, a drop in chirality transfer is observed, 90:10 e.r (entry 6). A change in the heteroatom from *O* to *N* in **(*R*)-206e** resulted in a high yield of product **(*S*)-207el**, 81% yield in a 97:3 e.r (entry 7). However, by once again inserting an extra CH_2 and moving the NPhthalate functional group further away from the allene, a noticeable drop in chirality transfer is observed, 81:19 e.r (entry 8). Until this point all examples (entries 1-7) produced only one regioisomer. However, allene **(*R*)-206f** produced two regioisomers in a 9:1 ratio (entry 8). This suggests that the functionality on the allene substituent is indeed responsible for the excellent regioselectivities observed.

The ester **(*R*)-206g** and Weinreb amide **(*R*)-206h** substituted allenes were then investigated (entries 9-11). Once again, the expected products **(*S*)-207gn** and **(*S*)-207go** were formed in excellent yields and enantiomeric ratios (92%, 97:3 e.r and 71%, 95:5 e.r respectively, entries 9 and 10). Allene **(*R*)-206h** containing the Weinreb amide substituent produces product **(*S*)-207hl** with a good e.r, 91:9 but with a slightly lower yield, 58% (entry 11). Moving the ester group one carbon further along the chain once again causes a drop in chirality transfer, 90:10 e.r, but still produces product **(*S*)-207il** in excellent regioselectivity (entry 12). However, having the ester group in conjugation with the allene **(*R*)-206j** proves to be detrimental to the reaction (entry 13).

Having demonstrated good regioselectivities with functionalised allenes, unfunctionalised allenes were next investigated. Aryl substituted allene **(*S*)-196**, originally investigated by Yamamoto[3a], gave a good regioselectivity, 10:1, but still racemised under these conditions (entry 14). It is likely the aryl substituent renders the allene isomerisation too rapid for successful chirality transfer under gold-catalysed hydroalkoxylation conditions.[8] The 1,3-dialkyl allene **(*S*)-206k** was studied next (entry 15). It was hoped that replacing the methyl group with a sterically hindered cyclohexane ring on allene **(*S*)-206k** would result in good regioselectivity through steric differentiation. However, this was not the case and the reaction resulted in two

regioisomers **207k** and **207k'** in a poor 1:0.7 ratio as an inseperable mixture (entry 15). However, the need for functionalised substituents to give good selectivity is not necessarily a drawback as they are much more useful in subsequent synthesis.

In order to investigate the minimum amount of functionality required to impart good regioselectivity, ether allene **(*S*)-206l** was investigated next (entry 16). The reaction is regioselective and produces product **(*R*)-207ll** with a decent e.r, 87:13 (entry 16). This suggests that some functionality on one substituent is required for good regio- and stereoselectivities and that the heteroatom and carbonyl plays a role in the observed selectivity.

6.3.3 Nucleophile Scope

The nucleophile scope was then investigated using allene **(*S*)-193** as the substrate (Table 6.11).

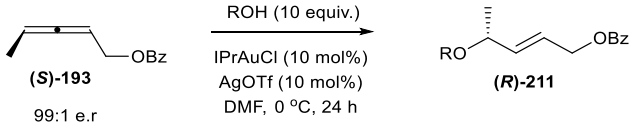
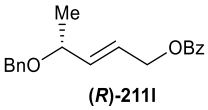
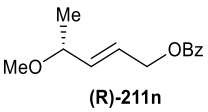
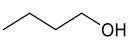
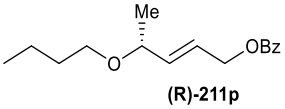
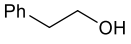
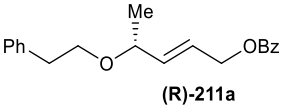
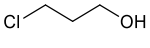
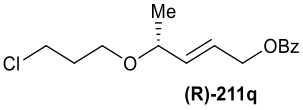
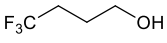
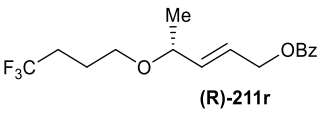
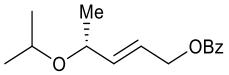
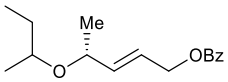
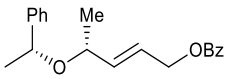
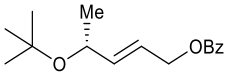
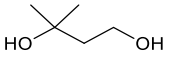
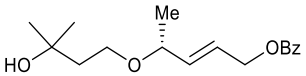
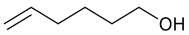
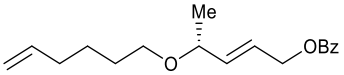
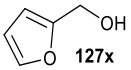
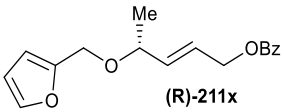
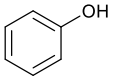


Table 6.11: Nucleophile scope

Entry	Alcohol	Product	Result[a]
1	 **127l**	 **(*R*)-211l**	65% 98:2 e.r[b]
2	MeOH **127n**	 **(R)-211n**	81% >95:5 e.r[c]
3	 **127p**	 **(R)-211p**	68% 97.5:2.5 e.r[b]
4	 **127a**	 **(R)-211a**	62% 98:2 e.r[b]
5	 **127q**	 **(R)-211q**	60% 97:3 e.r[b]
6	 **127r**	 **(R)-211r**	37% 99:1 e.r[b]

7	 **127m**	 **(R)-211m**	88% 97:3 e.r[b]
8	 **127s**	 **(R)-211s**	78% 81:19 e.r[b]
9	 **127t**	 **(R)-211t**	51% 97:3 e.r[b]
10	 **127u**	 **(R)-211u**	30% 94:6 e.r[b]
11	 **127v**	 **(R)-211v**	60% 98:2 e.r[b]
12	 **127w**	 **(R)-211w**	66% 98.8:0.2 e.r[b]
13	 **127x**	 **(R)-211x**	64% 99:1 e.r[b]
14	 **127y**	N/A	No reaction

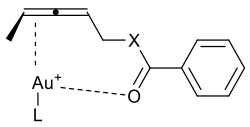
[a]Isolated yields, >20:1 *E/Z* and regioselectivity by ^{1}H NMR analysis unless otherwise stated. [b]Determined by CSP-HPLC. [c]Determined by ^{1}H NMR using chiral shift reagent (*R*)-(-)-1-(9-Anthryl)-2,2,2-trifluroethanol.

Primary benzyl alcohol **127l** and phenethyl alcohol **127a**, as well as alkyl alcohols including MeOH **127n** and *n*-butanol **127p** react well to produce the desired products in good to excellent yields (62-81%) and enantioselective ratios, >95:5 (entries 1-4). Primary alkyl alcohols with electron-withdrawing Cl (**127q**) and CF_3 (**127r**) also produce the desired products with excellent e.r, >97:3, but with slightly lower yields, 60% and 37% respectively (entries 5-6). Slightly more sterically hindered secondary alcohols react well, with *i*PrOH producing product **(*R*)-211m** in an excellent yield, 88%, and e.r, 97:3 (entry 7). Homochiral secondary alcohols **127s** and **127t** also proceed with good e.r, although the yield is slightly lower for the more sterically hindered alcohol **127t** (51%) *vs* **127s** (78%) (entries 8-9). Hence, the more sterically hindered *t*-BuOH produces only a 30% yield of the desired product but still proceeds with good chirality transfer, 94:6 e.r

(entry 10). This difference in reactivity can be exploited for the chemoselective reaction of unprotected diol **127v** to produce product **(*R*)-211v** in a 60% yield with a 98:2 e.r (entry 11). Other potentially sensitive functional groups are also tolerated including a pendent alkene **127w**, and a furan **127x** (entries 12-13). The less nucleophilic phenol **127y** is not a viable nucleophile in this reaction (entry 14).

6.3.4 Mechanistic Studies

From the substrate scope, it was ascertained that some degree of functionality is required to impart good regio- and stereoselectivity. It was therefore initially proposed that the Au(I) catalyst could be chelating to the functional group, whether it be O, N, or carbonyl, and thus providing the excellent enantioselectivities observed (Figure 6.2).



212

Figure 6.2 Possible chelation control through Au(I) catalyst?

However, our collaborators, Dr. David Johnson and Prof. Stuart Macgregor, carried out DFT caluculations which suggest the the proposed intermediate **212** is energetically highly unlikely. Instead, they propose that a second Ag^+ or a "naked" Au^+ ion could chelate to account for the selectivity observed (Figure 6.3, functional BP86, basis set SDDALL on Au(I) and 6-31G on all other atoms).

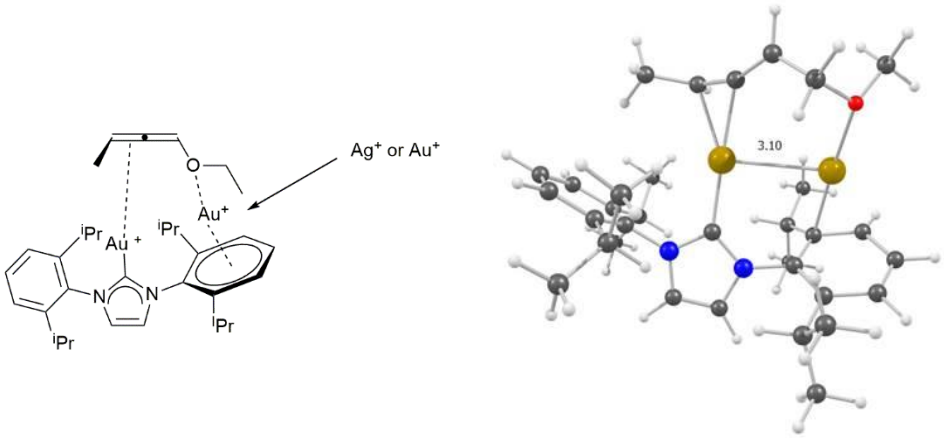
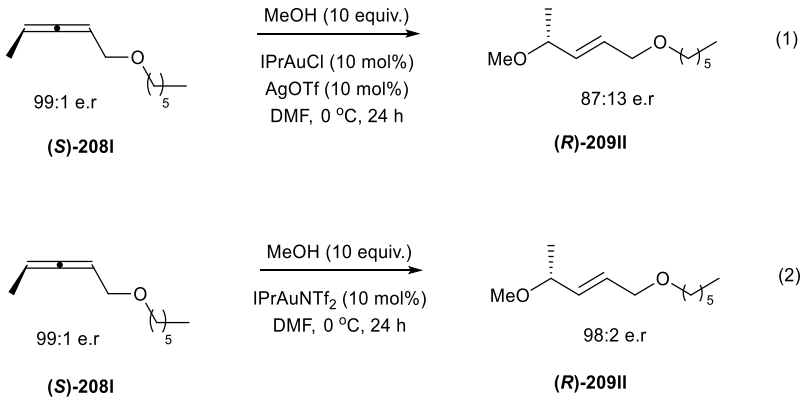


Figure 6.3: Initial hypothesis involving the chelation of a second "naked" Au^+ cation to account for selectivities observed.

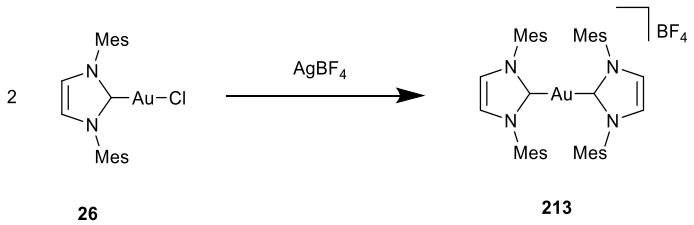
In order to prove this experimentally, a control reaction was carried out by Daniel Sutherland using a silver free gold(I) catalyst $IPrAuNTf_2$ (Scheme 6.19). If the reaction did indeed require the Ag^+ ion, a drop in regio- or stereoselectivity would be observed.



Scheme 6.19: Observations of regio- and stereoselectivity using a silver free catalyst.

Upon using the silver free catalyst, $IPrAuNTf_2$, an increase in stereoselectivity was in fact observed, which disproves the Ag^+ ions chelating theory. This leaves the possibility that a "naked" Au^+ ion could be potentially formed *in situ* and help with chelation control.

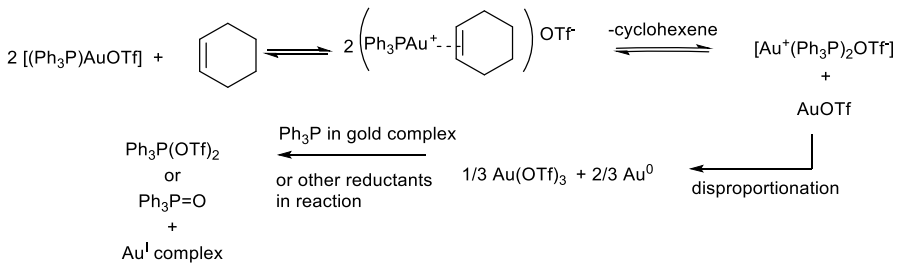
Albrecht and co-workers have recently suggested that the NHC-Au bond may be more labile than previously thought.[12] In the presence of $AgBF_4$, NHC complex **26** is able to undergo ligand redistribution to yield cationic complex **213** as a result of carbene transfer (Scheme 6.20). Therefore naked Au^+ ions could potentially be formed *in situ*.



26 **213**

Scheme 6.20: Carbene transfer reaction.

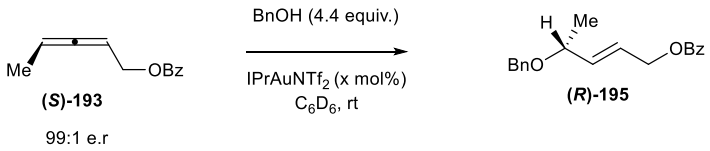
A second paper by Xu and co-workers also propose the formation of Au^+ ions *in situ*, but through a disproportionation reaction of the gold(I) catalyst in the presence of alkyne, alkene or allene substrates (Scheme 6.21).[13]



Scheme 6.21: Formation of Au^+ ions *in situ*.

Since Albrecht and Xu have both postulated the formation of Au^+ ions *in situ*, it is possible that it could also be generated in this reaction and could therefore be chelating the ligand of the gold(I) catalyst and the functional group of the allene. In order to prove this experimentally, a series of kinetic studies were carried out using NMR to ascertain whether the reaction is 2nd order with respect to the gold, and therefore provide evidence for Figure 6.3.

Due to cost of deuterated DMF, benzene-d_6 was used instead. Widenhoefer's conditions were used with the OBz substrate **(*S*)-193** (Scheme 6.22) since this substrate showed little to no difference in changing between the Widenhoefer method and our optimised conditions. The silver free catalyst $IPrAuNTf_2$ was used for practical reasons to avoid the formation of silver chloride precipitation during the NMR studies.



Scheme 6.22: Reaction scheme for kinetic studies.

The order of the $IPrAuNTf_2$ was determined by monitoring the rate of disappearance of allene against time at 5-20 mol% catalyst loadings, following a similar procedure used by Toste and co-workers.[4]

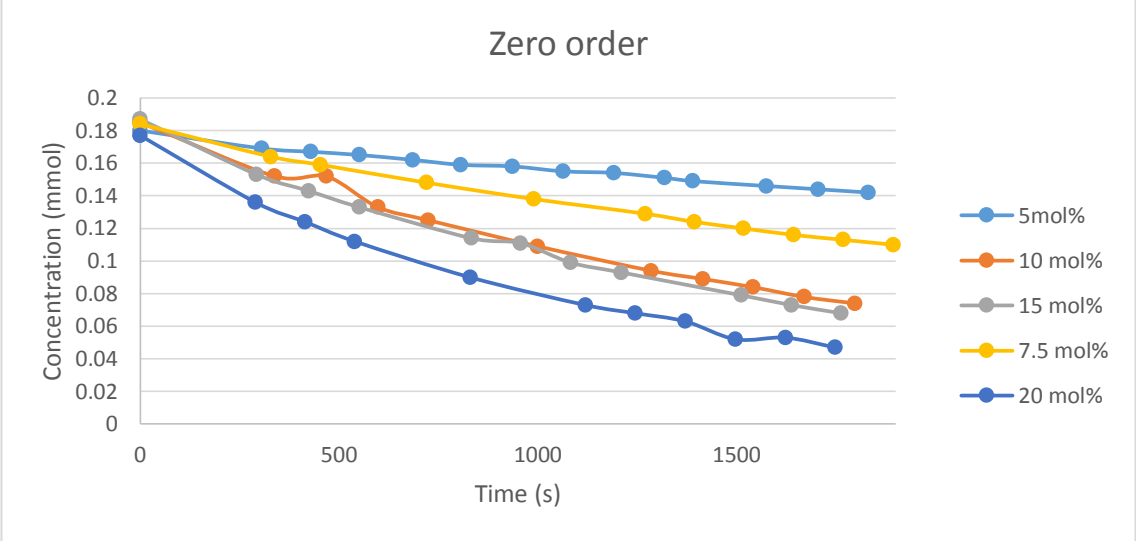


Figure 6.4: Concentration of allene **(*S*)-193** against time at different catalyst loadings.

As expected, the rate of reaction increases with increasing catalyst loadings (Figure 6.4). These results were then plotted for a 1st order reaction (Figure 6.5). Whilst the slope of the line varies with catalyst loadings, the plots are linear at all catalyst concentrations. This suggests that the reaction is first order with respect to the allene.

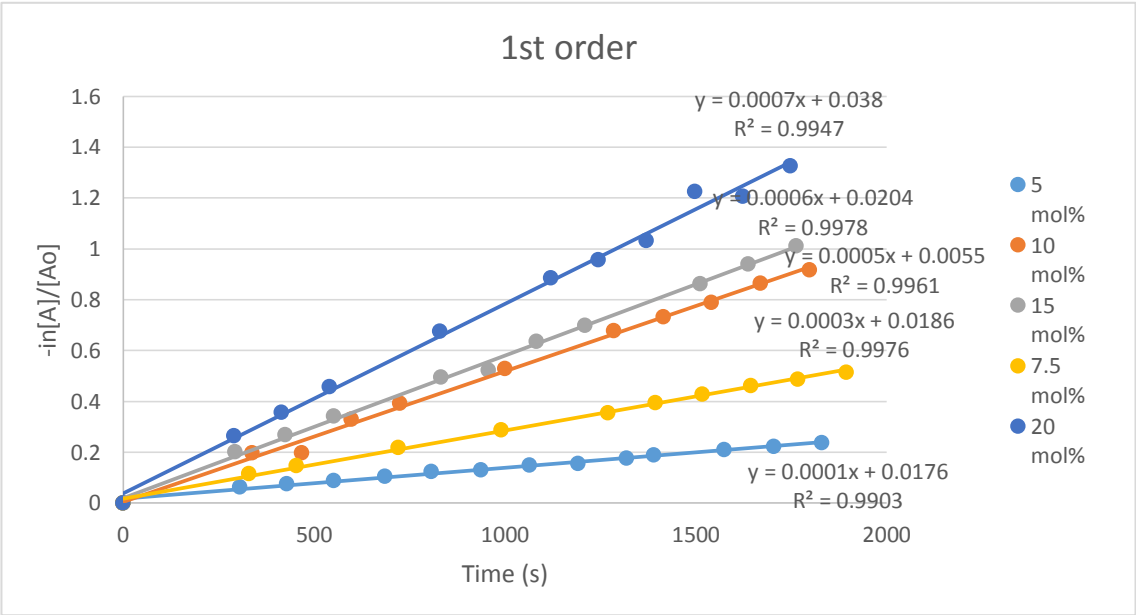


Figure 6.5: Plot natural log of concentration against time.

To obtain the order of the reaction with respect to the catalyst, each catalyst rate constant (K_{obs}) was obtained from the slope of ln([A]/[A_0]) *vs* time plot at 5-20 mol% catalyst loadings. A plot of K_{obs} against [Au] provided a straight line suggesting a first order dependence for the Au(I) catalyst (Figure 6.6).

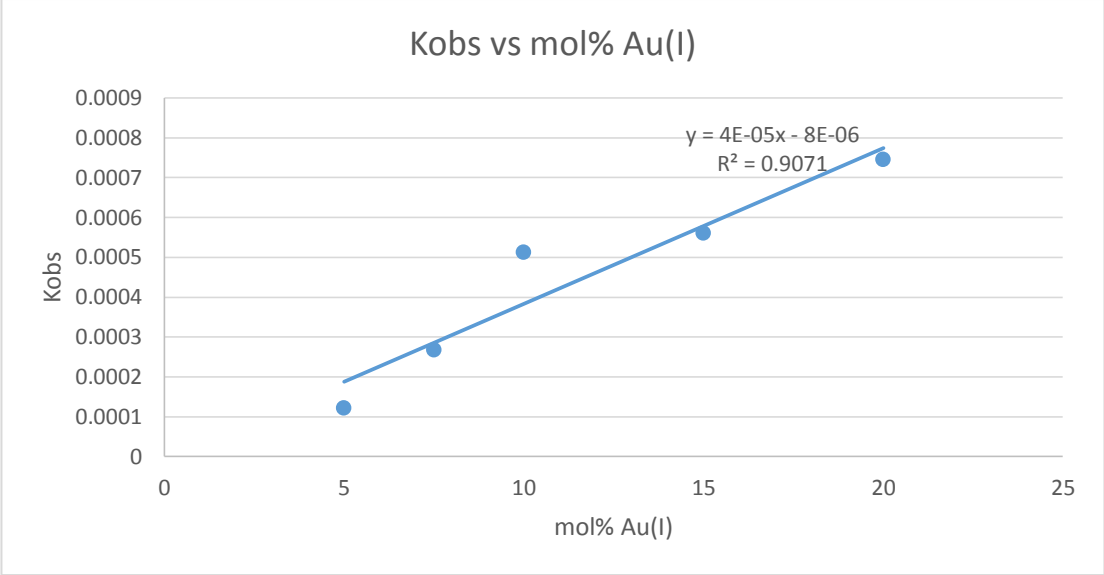


Figure 6.6: Plot of K_{obs} *vs* [Au].

The findings of the kinetics studies show a first order dependence of the Au(I) catalyst. Therefore, the chelation control model shown in Figure 6.3 cannot be in operation.

Instead, the regiochemistry observed may be due to an inductive effect, where the electron-withdrawing nature of the function group X results in an electronic differentiation between π-bonds a and b (Figure 6.7). Investigations are currently being carried out on allene **(*S*)-215** by Daniel Sutherland (Figure 6.7). By placing CF_3 at one end of the allene an inductive effect is created whilst avoiding any potential chelation. So far, these results show excellent regioselectivity and investigations into the enantioenriched allene are currently ongoing.

214 **(*S*)-215**

Figure 6.7: Allene **(*S*)-215** to test whether selectivity is purely down to inductive effects.

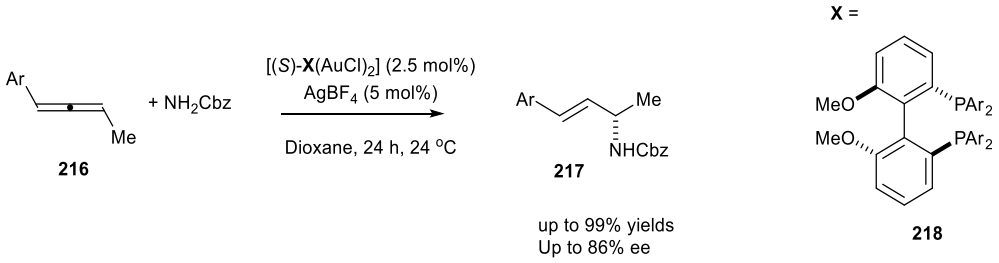
6.4 Conclusions

Gold(I)-catalysed hydroalkoxylation of 1,3-disubstituted allenes with efficient chirality transfer has been successfully developed. This reaction occurs with a wide range of substrates but does require some functionality on the allene substituent to provide excellent regio- and stereoselectivity.

Whilst the original idea of using molecular sieves to improve the chirality transfer failed, it was successfully shown that lowering the temperature of the reaction and using DMF as a solvent, greatly improved the e.r of the products by reducing the gold-catalysed racemisation of the allene substrates.

6.5 Future Work

In 2012, Widenhoefer and co-workers published a paper on the enantioselective hydroaminations of chiral, racemic 1,3-disubstitued allenes in a dynamic kinetic resolution (Scheme 6.23).[14] Various aryl substituted allenes **216** provided good yields and ee. Replacing the phenyl ring with a cyclohexyl ring was also tolerated. However, the Au(I)-catalysed hydroamination reaction with allenes lacking a methyl substituent was not effective.

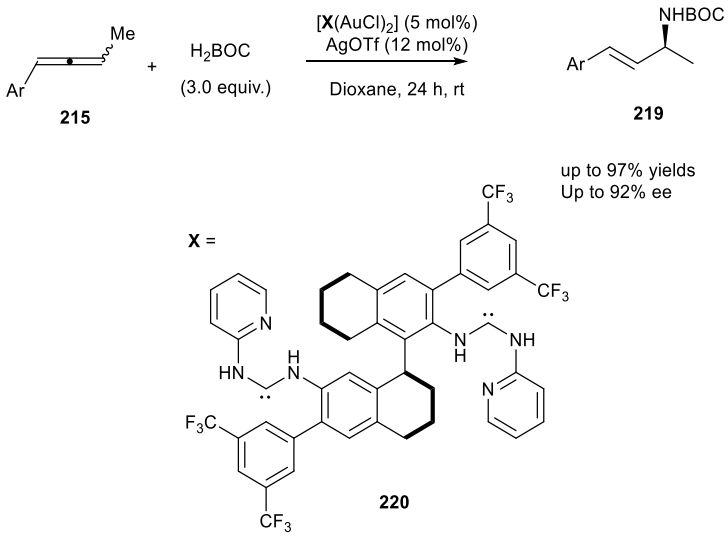


216 217 218

up to 99% yields
Up to 86% ee

Scheme 6.23: Widenhoefer's hydroamination of chiral, racemic 1,3-disubstituted allenes.

Recently Toste and co-workers have further investigated this work (Scheme 6.24). They also obtained good yields and enantioselectivity in the formation of allylic amines. However, they found that ligand **220** produced the best results. In contrast to the work by Widenhoefer, 1,3-disubstituted allenes containing alkyl groups other than Me were tolerated.[15]



215 219 220

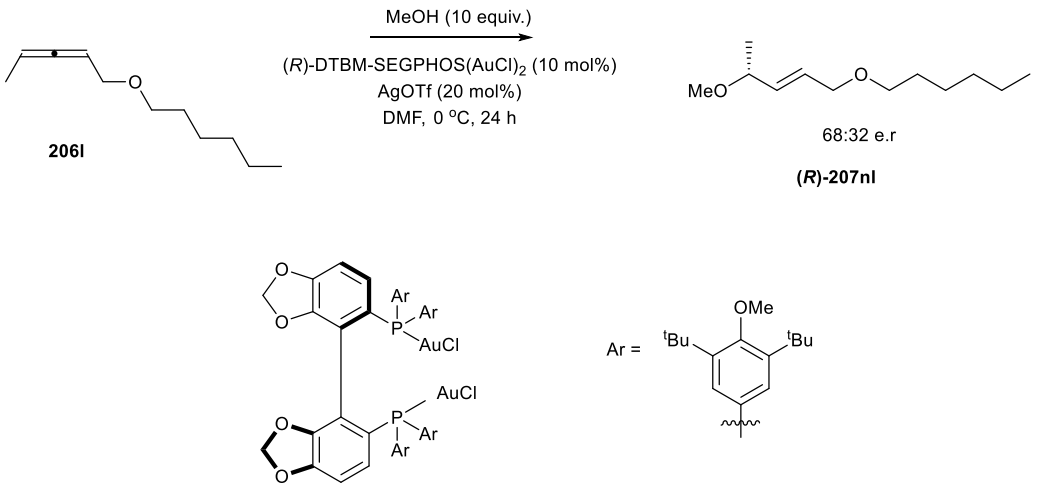
up to 97% yields
Up to 92% ee

Scheme 6.24: Toste's hydroamination of chiral, racemic 1,3-disubstituted allenes.

These types of reactions represent an attractive atom-economical approach to allylic amine derivatives. Having successfully carried out the chirality transfer in the

hydroalkoxylation reaction of allenes, it was speculated whether these reactions could be extended to alcohol nucleophiles.

Our initial test reaction involved the use of allene **206l** and SEGPHOS Au(I)-catalyst. Using our previous conditions, this produced product **(*R*)-207ln** in a moderate e.r, 68:32. Since the initial reaction looks promising, further investigations are currently ongoing.



Scheme 6.25: Initial reaction

6.6 Experimental

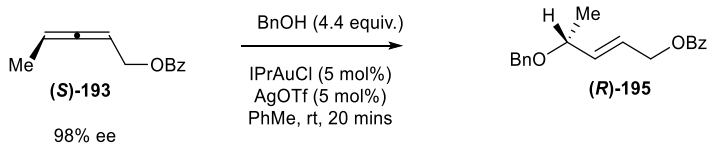
General Experimental Section

^{1}H NMR spectra was recorded on Bruker AV 300 and AV 400 spectrometers at 300 and 400 MHz respectively and referenced to residual solvent. ^{13}C NMR spectra were recorded using the same spectrometers at 75 and 100 MHz respectively. Chemical shift data are quoted in parts per million (ppm) and are referenced to tetramethylsilane (TMS) or to residual solvent peaks ($CDCl_3$ at δ_H 7.26). *J* values are given in Hz and s, d, dd, dt, ddt, dtd, t, td, tt, q, qd, qt, qn and m abbreviations correspond to singlet, doublet, doublet of doublet, doublet of triplet, doublet of doublet of triplet, doublet of triplet of doublet, triplet, triplet of doublet, triplet of triplet, quartet, quartet of doublet, quartet of triplet, quintet and multiplet. Mass spectra were obtained at the EPSRC National Mass Spectrometry Service Centre in Swansea and APCI represents atmospheric pressure chemical ionisation. Infrared spectra were obtained on Perkin-Elmer Spectrum 100 FT-IR Universal ATR Sampling Accessory, deposited neat or as a chloroform solution to a diamond/ZnSe plate. Flash column chromatography was carried out using Matrix silica gel 60 from Fisher Chemicals and TLC was performed using Merck silica gel 60 F254 pre-coated sheets and visualised by UV (254 nm) or stained by the use of aqueous acidic $KMnO_4$ or aqueous acidic ceric ammonium molybdate as appropriate. Chemicals were purchased from Sigma-Aldrich, Acros, Fisher and Apollo chemical companies and used without further purification unless otherwise stated. THF, DCM and DMF were dried using an MBRAUN SPS-800 solvent purification system. Diethyl ether was purified by distilling over CaH. High performance liquid chromatography (HPLC) was carried out on Agilent Technologies 1120 Compact LC. Gas chromatography was carried out on a Shimadzu GC2014 with FID.

The gold(I)-catalysed reactions were carried out in screw cap 1 dram vials unless otherwise indicated. No special precautions were taken to exclude air.

Determination of Absolute Configuration

Widenhoefer has previously shown that under the conditions shown in the scheme below, the *R*-enantiomer is produced. This was determined by comparing product **(*R*)-195** to known compounds.[2]



The conditions were repeated and produced the following HPLC trace (Figure 1).

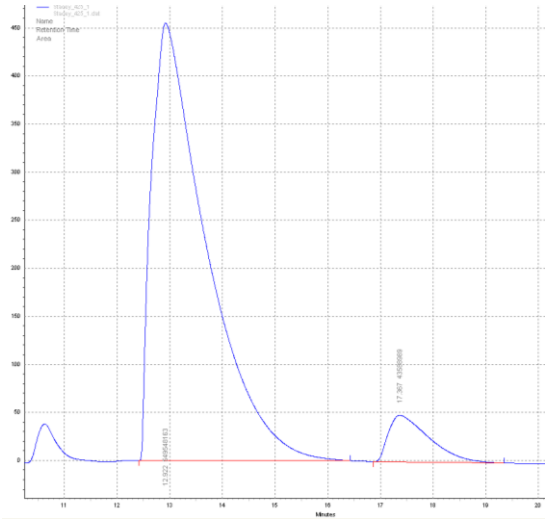


Figure 1: HPLC trace of product **(*R*)-195** obtained under Widenhoefer's conditions.

Under our conditions the following HPLC trace was obtained (Figure 2). This suggests our conditions are also producing the *R*-enantiomer of **195**. The absolute stereochemistry of the other products have been assigned by analogy.

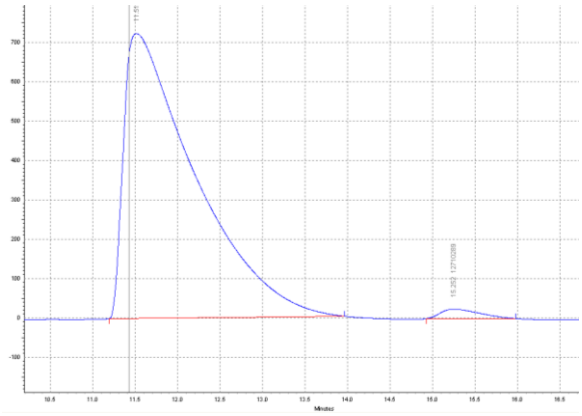
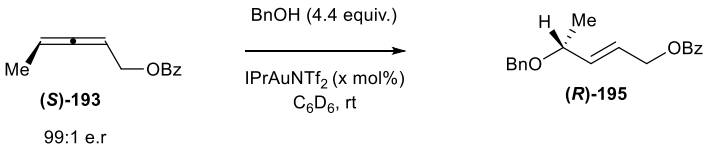


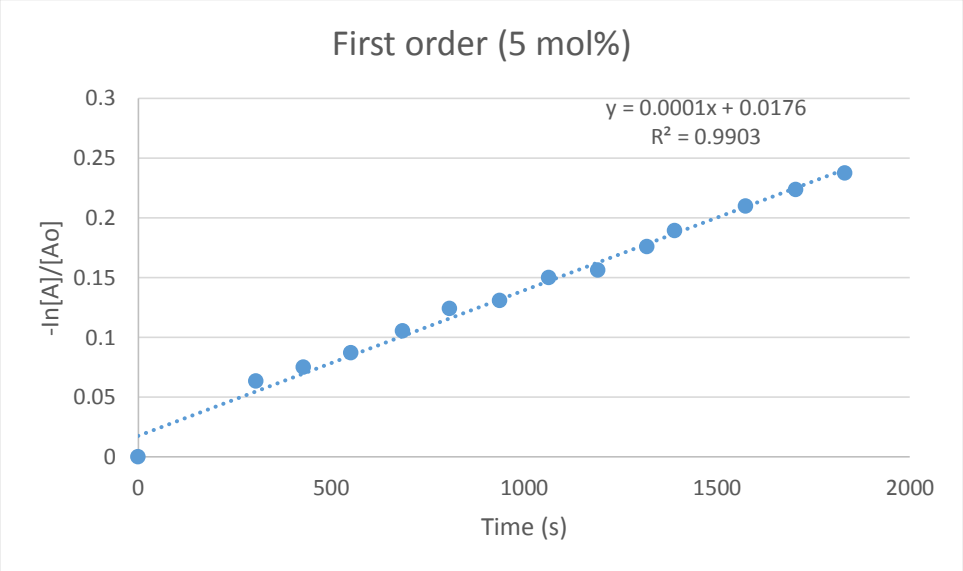
Figure 2: HPLC trace of product **(*R*)-195** under our conditions.

Determining the order of Au(I) catalyst

5 mol%



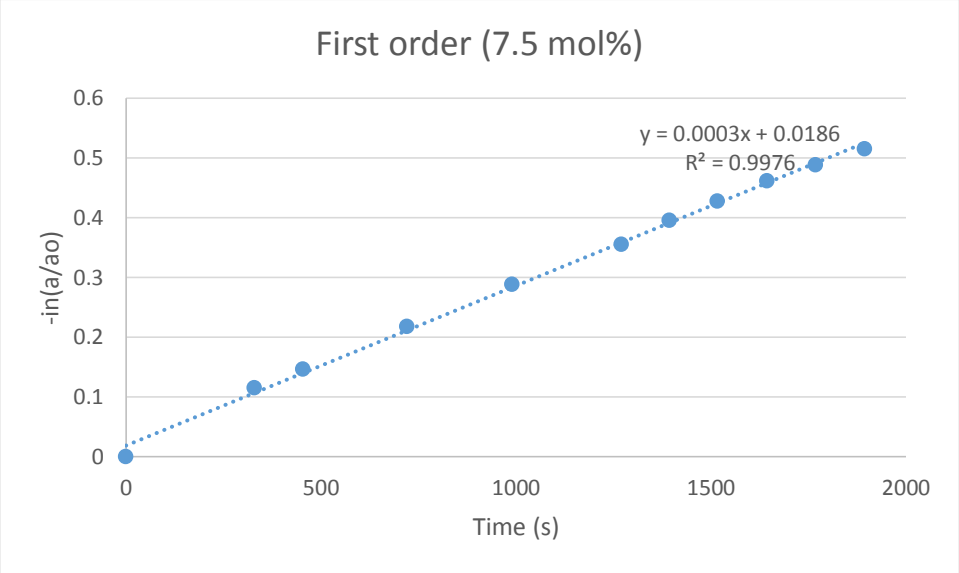
Time (s)	Conc. Of allene (mmol)	-In[A/Ao]
0	0.18	0
306	0.169	0.063058136
429	0.167	0.074963038
552	0.165	0.087011377
686	0.162	0.105360516
807	0.159	0.124052649
937	0.158	0.130361818
1064	0.155	0.149531734
1192	0.154	0.156004248
1319	0.151	0.175677014
1390	0.149	0.189010545
1575	0.146	0.209350229
1705	0.144	0.223143551
1831	0.142	0.237129793



Slope	0.000121697	0.017578	intercept
error in slope	3.47251E-06	0.003888	error in intercept
r^2	0.990324214	0.006909	s(y)
F	1228.209344	12	degrees of freedom
regression ss	0.058621149	0.000573	residual ss

7.5 mol%

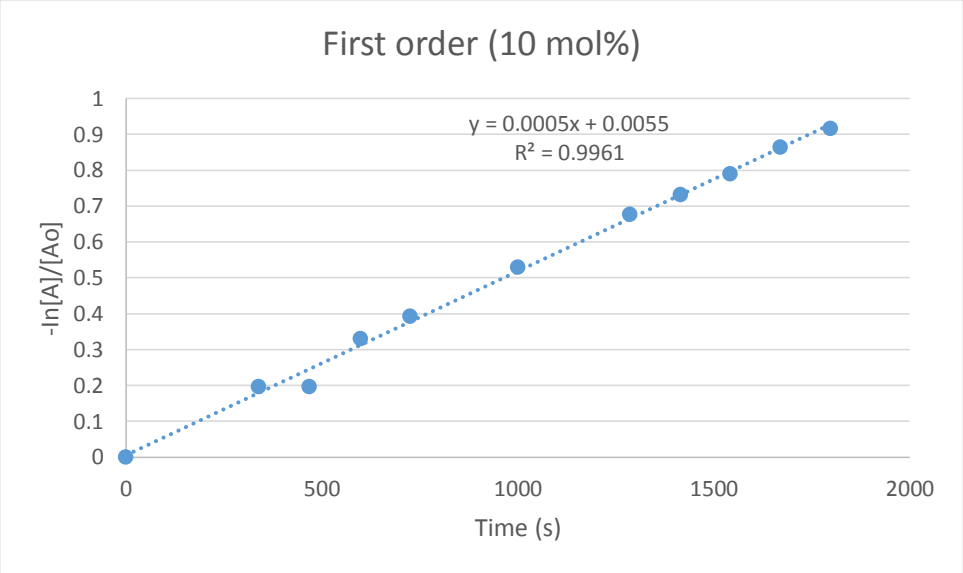
Time (s)	Conc. Allene (mmol)	-in[A/Ao]
0	0.184	0
329	0.164	0.11506933
454	0.159	0.146031555
721	0.148	0.217723484
990	0.138	0.287682072
1270	0.129	0.355123353
1394	0.124	0.394654192
1517	0.12	0.427444015
1644	0.116	0.461345567
1768	0.113	0.487547939
1894	0.11	0.514455392



Slope	0.000267313	0.018582	intercept
error in slope	4.32783E-06	0.005394	error in intercept
r^2	0.997646458	0.008697	s(y)
F	3815.024298	9	degrees of freedom
regression ss	0.288541493	0.000681	residual ss

10 mol%

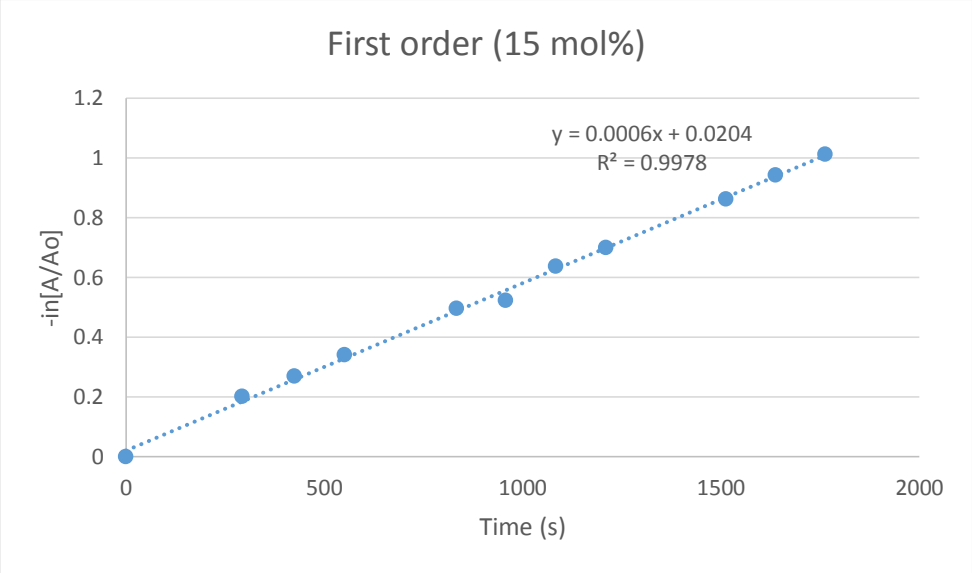
Time (s)	Conc. Of allene (mmol)	-In[A/Ao]
0	0.185	0
338	0.152	0.196475304
468	0.152	0.196475304
598	0.133	0.330006697
725	0.125	0.392042088
1000	0.109	0.529007943
1286	0.094	0.677061043
1415	0.089	0.731719455
1541	0.084	0.789539026
1670	0.078	0.863646998
1798	0.074	0.916290732



Slope	0.000513163	0.005462	intercept
error in slope	1.0715E-05	0.012204	error in intercept
r^2	0.996091459	0.020298	s(y)
F	2293.649272	9	degrees of freedom
regression ss	0.94499604	0.003708	residual ss

15 mol%

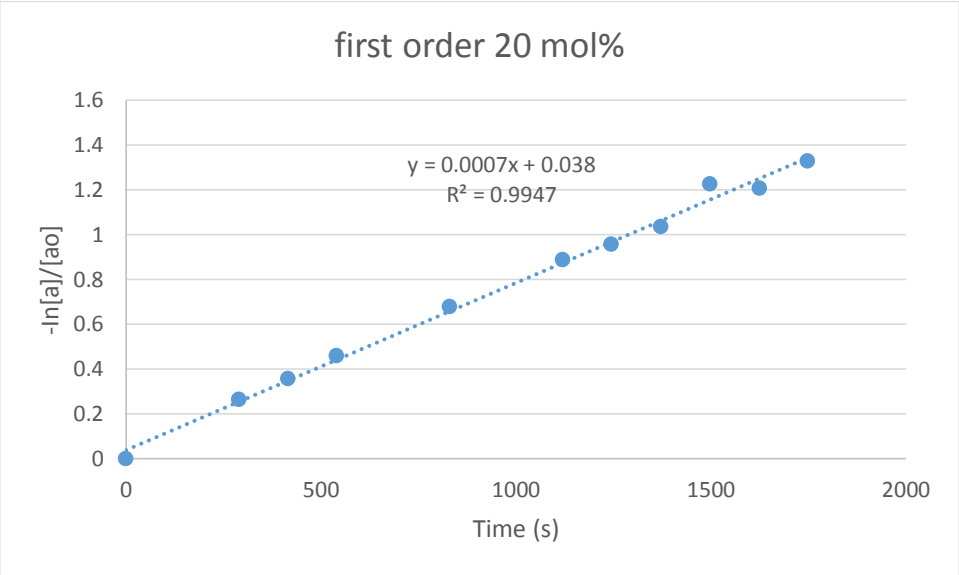
Time (s)	conc. Allene (mmol)	-in[A/Ao]
0	0.187	0
293	0.153	0.200670695
424	0.143	0.268263987
551	0.133	0.340759489
833	0.114	0.494910168
957	0.111	0.521578416
1083	0.099	0.635988767
1210	0.093	0.698509124
1512	0.079	0.861660764
1638	0.073	0.940649176
1763	0.068	1.011600912



Slope	0.000560276	0.020356	intercept
error in slope	8.84358E-06	0.009574	error in intercept
r^2	0.99776271	0.016104	s(y)
F	4013.723216	9	degrees of freedom
regression ss	1.040942989	0.002334	residual ss

20 mol%

Time (s)	Conc. (mmol)	-in[A/Ao]
0	0.177	0
290	0.136	0.263494847
415	0.124	0.355868167
540	0.112	0.457650861
830	0.09	0.676340062
1120	0.073	0.885690291
1245	0.068	0.956642027
1371	0.063	1.033015006
1498	0.052	1.224906014
1624	0.053	1.205857819
1748	0.047	1.326002131

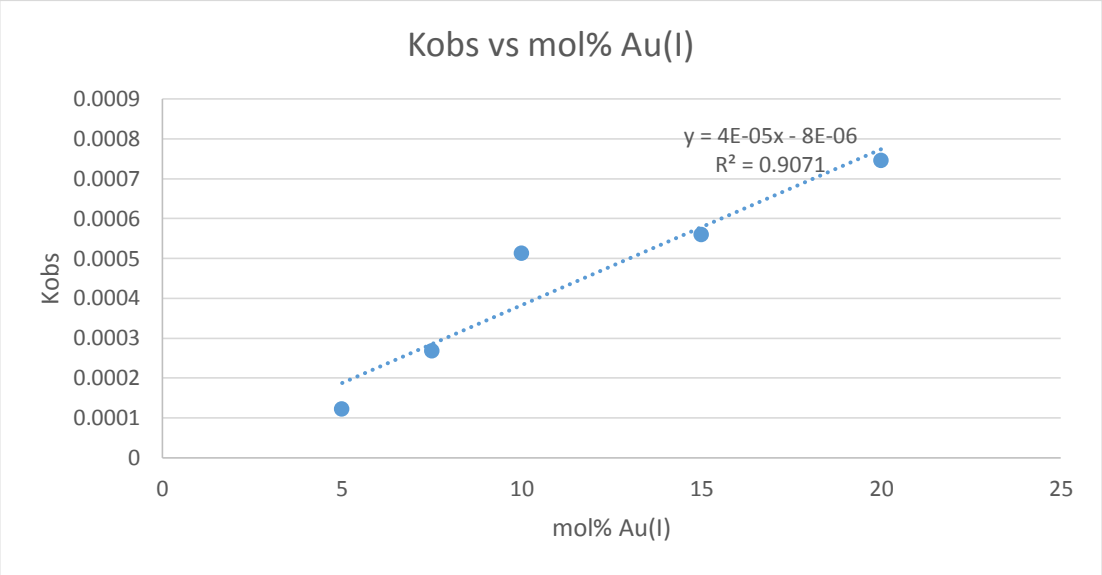


Slope	0.00074591	0.038036	intercept
error in slope	1.80684E-05	0.02028	error in intercept
r^2	0.994746857	0.033738	s(y)
F	1704.260162	9	degrees of freedom
regression ss	1.939839403	0.010244	residual ss

Data used to plot graphs 6.4 and 6.5 on page 234.

Following kinetics procedure from Toste and co-workers.[4]

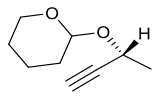
Mol%	Kobs
5	0.000121697
7.5	0.000267313
10	0.000513163
15	0.000560276
20	0.00074591



Slope	3.91115E-05	-8.11097E-06	intercept
error in slope	7.22628E-06	9.17624E-05	error in intercept
r2	0.907103817	8.70159E-05	s(y)
F	29.29411469	3	degrees of freedom
regression ss	2.21808E-07	2.27153E-08	residual ss

Characterisation

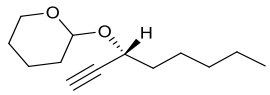
2-(((*R*)-But-3-yn-2-yl)oxy)tetrahydro-2*H*-pyran ((*R*)-221)[2]



To a solution of (*R*)-1-Butyn-3-ol (1.83 g, 26.1 mmol, 1 equiv., 97% ee), 3,4-dihydro-2H-pyran (2.9 ml, 31.3 mmol, 1.2 equiv.) and DCM (20 ml) at 0 °C were added TsOH (69 mg, 1.5 mol%). The solution was stirred for 2 hours at 0 °C. The reaction mixture was diluted with Et_2O, quenched with a saturated solution of $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent 10:1 pentane:ether) to yield product **(*R*)-221** as a colourless oil (3.56 g, 23.1 mmol, 89%) in a 1:0.9 mixture of diastereomers.

R_f 0.64 (15:1 pentane/Et_2O); ν_{max}/cm^{-1} 3291 (C≡C-H), 2940, 2870 (C-H), 1162 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 4.93 (1H, dd, *J* = 4.3, 2.9 Hz, OC<u>H</u>O, major), 4.76 (1H', t, *J* = 3.2 Hz, OCHO, minor), 4.54 (1H, qd, *J* = 6.7, 2.0 Hz, $CH_3C\underline{H}$, major), 4.45 (1H', qd, *J* = 6.7, 2.2 Hz, $CH_3C\underline{H}$, minor), 3.93-4.03 (1H', m, OCHC<u>H</u>$_2CH_2$, minor), 3.76-3.86 (1H, m, OCHC<u>H</u>$_2CH_2$, major), 3.47-3.57 (1H + 1H', m, OCHC<u>H</u>$_2CH_2$, major + minor), 2.41 (1H', d, *J* = 2.2 Hz, C≡CH, minor), 2.35 (1H, d, *J* = 2.0 Hz, C≡CH, major), 1.76-1.81 (1H + 1H', m, alkyl H's, major + minor), 1.64-1.76 (1H + 1H', m, alkyl H's, major + minor), 1.49-1.64 (4H + 4H', m, alkyl H's, major + minor), 1.46 (3H, d, *J* = 6.7 Hz, C<u>H</u>$_3$CH, major), 1.43 (3H', d, *J* = 6.7 Hz, C<u>H</u>$_3$CH, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 97.3 (CH, minor), 96.1 (CH, major), 84.8 (C, minor), 83.8 (C, major), 72.6 (CH, major), 72.0 (CH, minor), 62.7 (CH, major), 62.4 (CH_2, minor), 62.3 (CH_2, major), 60.7 (CH, minor), 30.7 (CH_2, minor), 30.6 (CH_2, major), 25.6 (CH_2, major), 25.5 (CH_2, minor), 22.2 (CH_3, major), 21.9 (CH_3, minor), 19.6 (CH_2, major), 19.2 (CH_2, minor).

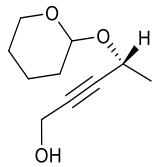
2-(((*R*)-Oct-3-yn-2-yl)oxy)tetrahydro-2*H*-pyran ((*R*)-222)[2]



To a solution of (*R*)-1-Octyn-3-ol (1.13 g, 8.92 mmol, 1 equiv., 97% ee), 3,4-dihydro-2H-pyran (1.0 ml, 10.7 mmol, 1.2 equiv.) and DCM (6.9 ml) at 0 °C were added TsOH (23 mg, 1.5 mol%). The solution was stirred for 2 hours at 0 °C. The reaction mixture was diluted with Et_2O, quenched with a saturated solution of $NaHCO_3$ and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent 10:1 hexane:ether) to yield product **(*R*)-222** as a colourless oil (1.76 g, 8.38 mmol, 94%) in a 1:0.3 mixture of diastereomers.

ν_{max}/cm^{-1} 3309 (C≡C-H), 2939, 2860 (C-H), 1157 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (1H, t, *J* = 2.9 Hz, OC<u>H</u>O, major), 4.75 (1H', t, *J* = 3.3 Hz, OC<u>H</u>O, minor), 4.41 (1H, td, *J* = 6.7, 2.0 Hz, OC<u>H</u>CH_2, major), 4.28 (1H', td, *J* = 6.7 Hz, 2.2 Hz, OC<u>H</u>CH_2, minor), 3.97-4.07 (1H', m, OC<u>H</u>$_2$$CH_2$, minor), 3.76-3.86 (1H, m, OC<u>H</u>$_2$$CH_2$, major), 3.49-3.59 (1H + 1H', m, OC<u>H</u>$_2$$CH_2$, major + minor), 2.43 (1H', d, *J* = 2.2 Hz, <u>H</u>C≡C, minor), 2.37 (1H, d, *J* = 2.0 Hz, <u>H</u>C≡C, major), 1.68-1.89 (4H + 4H', m, alkyl H's, major + minor), 1.42-1.67 (6H + 6H', m, alkyl H's, major + minor), 1.24-1.39 (4H + 4H', m, alkyl H's, major + minor), 0.87-0.97 (3H + 3H', m, CH_3, major + minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 98.3 (CH, minor), 95.7 (CH, major), 84.1 (C, minor), 83.1 (C, major), 73.2 (CH, major), 72.6 (CH, minor), 67.3 (CH, minor), 64.9 (CH, major), 62.5 (CH_2, major), 62.4 (CH_2, minor), 35.8 (CH_2, major), 35.7 (CH_2, minor), 31.7 (CH_2, major), 31.6 (CH_2, minor), 30.6 (CH_2, major + minor), 25.6 (CH_2, major), 25.5 (CH_2, minor), 25.2 (CH_2, major), 24.9 (CH_2, minor), 22.8 (CH_2, major), 22.7 (CH_2, minor), 19.5 (CH_2, major), 19.2 (CH_2, minor), 14.2 (CH_3, major), 14.1 (CH_3, minor).

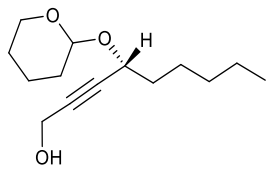
(4*R*)-4-((Tetrahydro-2*H*-pyran-2-yl)oxy)pent-2-yn-1-ol ((*R*)-223)[2]



n-BuLi (13 ml, 2.5 M in hexanes, 32.3 mmol, 1.4 equiv.) was added dropwise (over 20 mins) to a solution of **(*R*)-221** (3.56 g, 23.1 mmol, 1 equiv.) in THF (77 ml) at -78 °C under Ar. Allowed to warm to room temperature and paraformaldehyde (1.30 g, 43.0 mmol, 2.0 equiv.) was added. The reaction was stirred for a further 2 hours. The reaction mixture was diluted with Et_2O, quenched with a saturated solution of NH_4Cl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 10:1 then 1:1 hexane/Et_2O) to yield product **(*R*)-223** as a colourless oil as a 1:0.9 mixture of diastereomers (3.38 g, 18.3 mmol, 80%).

R_f 0.35 (1:1 hexane/Et_2O); ν_{max}/cm^{-1} 3416 (O-H), 2938, 2868 (C-H), 1114 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 4.92 (1H, t, *J* = 3.0 Hz, OC<u>H</u>O, major), 4.76 (1H', t, *J* = 3.1 Hz, minor), 4.57 (1H, qt, *J* = 6.7, 1.6 Hz, C<u>H</u>CH_3, major), 4.49 (1H', qt, *J* = 6.6, 1.7 Hz, C<u>H</u>CH_3, minor), 4.29 (2H', d, *J* = 1.6 Hz, HOC<u>H</u>$_2$, minor), 4.27 (2H, d, *J* = 1.7 Hz, HOC<u>H</u>$_2$, major), 3.93-4.02 (1H', m, OC<u>H</u>$_2CH_2$, minor), 3.76-3.85 (1H, m, OC<u>H</u>$_2CH_2$, major), 3.47-3.57 (1H + 1H', m, OC<u>H</u>$_2CH_2$, major + minor), 2.04-2.18 (1H + 1H', m, OH, major + minor), 1.79-1.90 (1H + 1H', m, alkyl H's, major + minor), 1.65-1.77 (1H + 1H', m, alkyl H's, major + minor), 1.48-1.65 (4H + 4H', m, alkyl H's, major + minor), 1.45 (3H, d, *J* = 6.7 Hz, CH_3, major), 1.42 (3H', d, *J* = 6.6 Hz, CH_3, minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 97.3 (CH, minor), 95.9 (CH, major), 86.5 (C, minor), 85.5 (C, major), 83.1 (C, major), 82.4 (C, minor), 62.7 (CH, minor), 62.6 (CH_2, major), 62.5 (CH_2, minor), 60.9 (CH, major), 51.2 (CH_2, minor), 51.1 (CH_2, major), 30.7 (CH_2, minor), 30.6 (CH_2, major), 25.53 (CH_2, major), 25.46 (CH_2, minor), 22.2 (CH_3, major), 21.9 (CH_3, minor), 19.5 (CH_2, major), 19.3 (CH_2, minor).

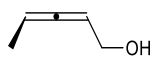
(4*R*)-4-((Tetrahydro-2*H*-pyran-2-yl)oxy)non-2-yn-1-ol ((*R*)-224)[2]



n-BuLi (6.6 ml, 1.6 M in hexanes, 10.6 mmol, 1.4 equiv.) was added dropwise (over 20 mins) to a solution of **(*R*)-222** (1.59 g, 7.57 mmol, 1 equiv.) in THF (20 ml) at -78 °C under Ar. The reaction mixture was allowed to warm to room temperature and paraformaldehyde (462 mg, 15.4 mmol, 2.0 equiv.) was added. The mixture was stirred for a further 2 hours. The reaction mixture was diluted with Et_2O, quenched with a saturated solution of NH_4Cl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 1:1 hexane/Et_2O) to yield product **(*R*)-224** as a colourless oil as a 1:0.1 mixture of diastereomers (1.42 g, 5.90 mmol, 78%).

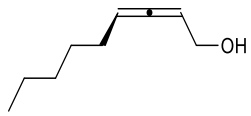
ν_{max}/cm^{-1} 3407 (O-H), 2931, 2859 (C-H), 1113 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 4.96 (1H, t, *J* = 2.9 Hz, OC<u>H</u>O), 4.44 (1H, tt, *J* = 6.7, 1.6 Hz, C<u>H</u>CH_2), 4.29 (2H, dd, *J* = 6.1, 1.6 Hz, HOC<u>H</u>$_2$), 3.75-3.85 (1H, m, OC<u>H</u>$_2CH_2$), 3.49-3.57 (1H, m, OC<u>H</u>$_2CH_2$), 1.67-1.86 (5H, m, alkyl H's), 1.42-1.64 (6H, m, alkyl H's), 1.26-1.36 (4H, m, alkyl H's), 0.89 (3H, d, *J* = 6.7 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 95.5 (CH), 85.0 (C), 83.6 (C), 65.0 (CH), 62.3 (CH_2), 51.3 (CH_2), 35.9 (CH_2), 31.7 (CH_2), 30.6 (CH_2), 25.6 (CH_2), 25.3 (CH_2), 22.7 (CH_2), 19.4 (CH_2), 14.2 (CH_3).

(*S*)-Penta-2,3-dien-ol ((*S*)-225)[2]



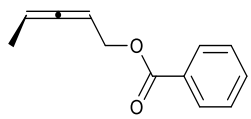
A solution of **(*R*)-223** (3.38 g, 18.3 mmol, 1.0 equiv.) in Et_2O (18 ml) was added to a solution of $LiAlH_4$ (1.26 g, 33.2 mmol, 1.8 equiv.) in Et_2O (30 ml) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction was then cooled to 0 °C and quenched with successive additions of water (4.0 ml), 15% NaOH (4.0 ml) and water (4.0 ml). The white suspension was filtered through celite, washed with Et_2O and then concentrated. The product was used without further purification.

(*S*)-Nona-2,3-dien-1-ol ((*S*)-226)[2]



A solution of **(*R*)-224** (1.42 g, 5.92 mmol, 1.0 equiv.) in Et_2O (8 ml) was added to a solution of $LiAlH_4$ (472 mg, 12.4 mmol, 2.0 equiv.) in Et_2O (8 ml) at 0 °C. The reaction mixture was slowly warmed to room temperature and stirred for 18 hours. The reaction was then cooled to 0 °C and quenched with successive additions of water (2.0 ml), 15% NaOH (2.0 ml) and water (2.0 ml). The white suspension was filtered through celite, washed with Et_2O and then concentrated. The product was used without further purification.

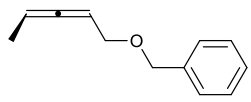
(*S*)-Penta-2,3-dien-1-yl benzoate ((*S*)-193)[2]



To a solution of **(*S*)-225** (1.02 g, 12.2 mmol, 1.0 equiv.) in DCM (50 ml) was added BzCl (3.0 ml, 24.6 mmol, 2.0 equiv.), pyridine (7.0 ml, 86.1 mmol, 7.0 equiv.) and 4-(dimethylamino)pyridine (306 mg, 2.5 mmol, 0.2 equiv.) at 0 °C. The solution was stirred for 6 hours. The reaction was quenched with 6N HCl and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 7:1 hexane:Et_2O) to give product **(*S*)-193** as a yellow oil (870.5 mg, 4.63 mmol, 38%, 98% ee).

R_f 0.4 (3:1 Hexane/Et_2O); ν_{max}/cm^{-1} 2948 (C-H), 1970 (C=C=C), 1716 (C=O), 1601, 1584, 1491,1451 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-8.09 (2H, m, Ar-H), 7.53-7.59 (1H, m, Ar-H), 7.41-7.47 (2H, m, Ar-H), 5.30-5.40 (1H, m, allene H), 5.21-5.30 (1H, m, allene H), 4.80 (2H, dd, *J* = 6.7, 2.4 Hz, CHC$\underline{H}_2$O), 1.69 (3H, dd, *J* = 7.0, 3.2 Hz, CHC$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.4 (C), 166.5 (C), 133.0 (CH), 130.4 (C), 129.8 (CH), 128.4 (CH), 87.9 (CH), 86.5 (CH), 63.4 (CH_2), 14.0 (CH_3); $[\alpha]_D^{22°C}$ = +33.6 (c = 1.07 in $CHCl_3$); CSP-GC (β-Dex, 120 °C, 35 cm s^{-1}) **(*R*)-193** 73.5 min and **(*S*)-193** 74.4 min.

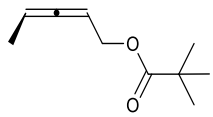
(*S*)-((Penta-2,3-dien-1-yloxy)methyl)benzene ((*S*)-209)



Compound **(*S*)-225** (311 mg, 3.70 mmol, 1.0 equiv.) was added dropwise to a solution of NaH (60% in oil, 216 mg, 5.55 mmol, 1.5 equiv.) in THF (3.7 ml) at room temperature followed by addition of BnCl (0.64 ml, 5.55, 1.5 equiv.). The reaction mixture was then stirred at 50 °C for 18 hours. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 50:1 then 25:1 hexane/Et_2O) to yield product **(*S*)-209** as a yellow oil (313.2 mg, 1.8 mmol, 49%, 98% ee).

R_f 0.37 (20:1 hexane/ Et_2O); ν_{max}/cm^{-1} 3029, 2924, 2855 (C-H), 1966 (C=C=C), 1495, 1453, 1410 (C-C Ar), 1093 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.39 (5H, m, Ar-H), 5.13-5.28 (2H, m, allene-H), 4.54 (2H, s, OC$\underline{H}_2$Ph), 4.05 (2H, dd, *J* = 6.4, 2.6 Hz, CHC$\underline{H}_2$O), 1.69 (3H, dd, *J* = 6.7, 3.5 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.0 (C), 138.4 (C), 128.5 (CH), 128.0 (CH), 127.7 (CH), 87.9 (CH), 86.7 (CH), 71.8 (CH_2), 68.6 (CH_2), 14.3 (CH_3); $[\alpha]_D^{21℃}$ = +31.9 (c = 1.06 in $CHCl_3$); CSP-GC (β-Dex, 110 °C, 35 cm s^{-1}) **(*R*)-209** 65.5 min and **(*S*)-209** 66.1 min.

(*S*)-Penta-2,3-dien-1-yl pivalate ((*S*)-206a)

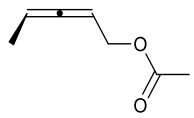


Compound **(*S*)-225** (309 mg, 3.68 mmol, 1.0 equiv.) was added dropwise to a solution of NaH (60% in oil, 222 mg, 5.55 mmol, 1.5 equiv.) in THF (3.7 ml) at room temperature followed by addition of PivCl (0.68 ml, 5.55, 1.5 equiv.). The reaction mixture was then stirred at 50 °C for 18 hours. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 25:1 hexane/Et_2O) to yield product **(*S*)-206a** as a yellow oil (303 mg, 1.8 mmol, 49%, 98% ee (%ee assumed from previous allenes as this allene cannot be separated by GC or HPLC)).

R_f 0.39 (25:1 hex/Et_2O); ν_{max}/cm^{-1} 2972 (C-H), 1971 (C=C=C), 1730 (C=O), 1032 (C-O-C); ^1H NMR (300 MHz, $CDCl_3$) δ 5.14-5.28 (2H, m, allene-H), 4.53 (2H, dd, *J* = 6.1, 3.0

Hz, C<u>H</u>$_2$O), 1.67 (3H, dd, *J* = 6.7, 3.5 Hz, CH_3), 1.20 (9H, s, ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.9 (C), 178.4 (C), 87.9 (CH), 86.8 (CH), 62.4 (CH_2), 38.9 (C), 27.3 (CH_3), 14.1 (CH_3); Found (GC/MS EI+) $[M]^+$ 168.1152, $C_{10}H_{16}O_2$ requires 168.1150. $[\alpha]_D^{21^\circ C}$ = +21.4 (c = 1.12 in $CHCl_3$).

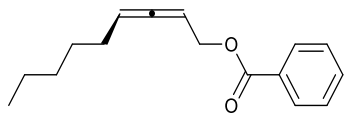
(*S*)-Penta-2,3-dien-1-yl acetate ((*S*)-206b)



Compound **(*S*)-225** (299 mg, 3.56 mmol, 1.0 equiv.) was added dropwise to a solution of NaH (60% in oil, 180 mg, 5.07 mmol, 1.5 equiv.) in THF (3.4 ml) at 0 °C followed by addition of AcCl (0.36 ml, 5.07, 1.5 equiv.). The reaction mixture was then stirred at 35 °C for 18 hours. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 10:1 hexane/Et_2O) to yield product **(*S*)-206b** as a yellow oil (92.3 mg, 0.73 mmol, 21%, 98% ee).

R_f 0.33 (10:1 hex/Et_2O); ν_{max}/cm^{-1} 2949 (C-H), 1970 (C=C=C), 1738 (C=O), 1022 (C-O-C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.15-5.30 (2H, m, allene H), 4.52-4.57 (2H, m, OCH_2), 2.06 (3H, s, O=CCH_3), 1.65-1.71 (3H, m, CHC<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 206.3 (C), 170.9 (C), 87.7 (CH), 86.4 (CH), 63.0 (CH_2), 21.1 (CH_3), 14.0 (CH_3); Found (GC/MS EI+) $[M]^+$ 126.0682, $C_7H_{10}O_2$ requires 126.0681; $[\alpha]_D^{21^\circ C}$ = +45.5 (c = 1.10 in $CHCl_3$); CSP-GC (β-Dex, 100 °C, 35 cm s^{-1}) **(*R*)-206b** 5.7 min and **(*S*)-206b** 5.8 min.

(*S*)-Nona-2,3-dien-1-yl benzoate ((*S*)-206c)[2]

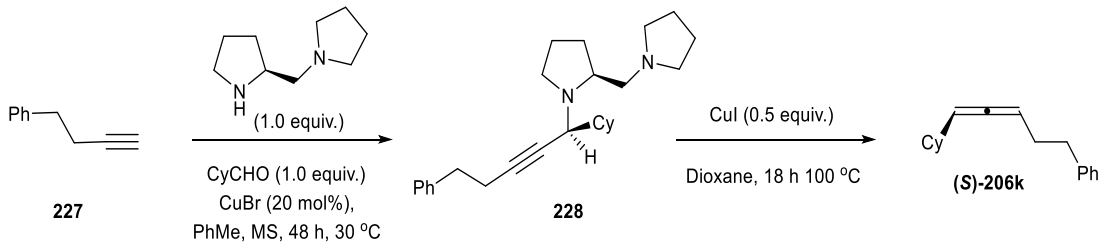


To a solution of **(*S*)-225** (481 mg, 3.45 mmol, 1.0 equiv.) in DCM (8.0 ml) was added BzCl (0.46 ml, 3.94 mmol, 1.1 equiv.), pyridine (1.1 ml, 13.8 mmol, 4.0 equiv.) and 4-(dimethylamino)pyridine (47.6 mg, 0.38 mmol, 0.1 equiv.) at 0 °C. The solution was stirred for 6 hours. The reaction was quenched with 6N HCl and extracted with Et_2O. The combined organic layers were washed with brine and then dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 10:1 then

7:1 hexane:Et_2O) to give product **(*S*)-206c** as a yellow oil (436 mg, 1.79 mmol, 52%, 98% ee). ee assumed from previous allene reactions as no separation conditions were found.

R_f 0.6 (5:1 Hexane/Et_2O); ν_{max}/cm^{-1} 2927, 2856 (C-H), 1965 (C=C=C), 1718 (C=O), 1601, 1584,1451 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-8.09 (2H, m, Ar-H), 7.52-7.59 (1H, m, Ar-H), 7.40-7.48 (2H, m, Ar-H), 5.23-7.42 (2H, m, allene H), 4.80 (2H, dd, *J* = 6.6, 2.4 Hz, CHC$\underline{H_2}$O), 2.02 (2H, app. qd, *J* = 6.9, 3.0 Hz, =CHC$\underline{H_2}$$CH_2$), 1.38-1.46 (2H, m, alkyl H's), 1.26-1.33 (4H, m, alkyl H's), 0.87 (3H, t, *J* = 7.0 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.6 (C), 166.5 (C), 133.0 (CH), 130.5 (C), 129.8 (CH), 128.4 (CH), 93.3 (CH), 87.1 (CH), 63.5 (CH_2), 31.4 (CH_2), 28.8 (CH_2), 28.5 (CH_2), 22.6 (CH_2), 14.2 (CH_3); $[\alpha]_D^{20°C}$ = +35.2 (c = 1.02 in $CHCl_3$).

(*S*)-(5-Cyclohexylpenta-3,4-dien-1-yl)benzene ((*S*)-206k)[16]



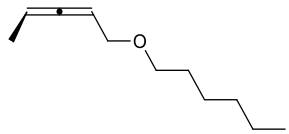
CuBr (58.0 mg, 20 mol%), (*S*)-(+)-1-(2-Pyrrolidinylmethyl)pyrrolidine (0.33 ml, 2.0 mmol, 1.0 equiv.) and dry toluene (3.0 ml) were added to a flask. Distilled cyclohexanecarboxaldehyde (0.24 ml, 2.0 mmol, 1.0 equiv.), 4 Å molecular sieves (1 g) and 4-phenyl-1-butyne (0.31 ml, 2.2 mmol, 1.1 equiv.) were added to the flask and stirred under Ar at 30 °C for 48 hours. The molecular sieves were removed *via* filtration and washed with Et_2O. The crude product was purified by column chromatography using basic alumina (eluent 40:1 hexane/EtOAc) to yield product **228** as an impure yellow oil (271 mg, 0.71 mmol 36%).

Compound **228** (271 mg, 0.72 mmol, 1.0 equiv.), freshly distilled dioxane (2.9 ml) and CuI (72.0 mg, 0.38 mmol, 0.5 equiv.) were added to a flask and refluxed for 18 hours. The crude was purified by column chromatography (eluent: hexane) to yield product **(*S*)-206k** as a yellow oil (57.4 mg, 0.25 mmol 35%).

R_f 0.48 (hexane); ν_{max}/cm^{-1} 2920, 2848 (C-H), 1959 (C=C=C), 1495, 1447 (C-C Ar); ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.25 (3H, m, Ar-H), 7.07-7.15 (2H, m, Ar-H), 5.04-5.13 (1H, m, Allene-H), 4.97-5.04 (1H, m, Allene-H), 2.59-2.70 (2H, m, alkyl-H), 2.17-2.29

(2H, m, alkyl-H), 1.76-1.91 (1H, m, alkyl-H), 1.49-1.68 (5H, m, alkyl-H), 1.07-1.26 (3H, m, alkyl-H), 0.87-1.07 (2H, m, alkyl-H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 202.9 (C), 142.1 (C), 128.7 (CH), 128.4 (CH), 125.9 (CH), 97.7 (CH), 91.3 (CH), 37.4 (CH), 35.7 (CH_2), 33.23 (CH_2), 33.20 (CH_2), 31.0 (CH_2), 26.3 (CH_2), 26.21 (CH_2), 26.20 (CH_2).

(*S*)-1-((3-Penta-2,3-dien-1-yl)oxy)hexane ((*S*)-206l)



Compound **(*S*)-225** (290 mg, 3.46 mmol, 1.0 equiv.) was added dropwise to a solution of NaH (60% in oil, 193 mg, 5.19 mmol, 1.5 equiv.) in THF (3.5 ml) followed by addition of iodohexane (0.56 ml, 3.80, 1.1 equiv.). The reaction mixture was then stirred at 50 °C for 18 hours. The reaction was quenched with water and extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated. The mixture was purified by column chromatography (eluent: 20: then 10:1 hexane/Et_2O) to yield product **(*S*)-206l** as a colourless oil (165 mg, 0.98 mmol, 28%, 98% ee).

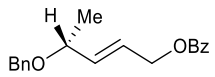
R_f 0.81 (3:1 hex/Et_2O); ν_{max}/cm^{-1} 2928, 2856 (C-H), 1967 (C=C=C), 1738 (C=O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.10-5.20 (2H, m, allene H), 3.93-3.99 (2H, m, =CHC$\underline{H}_2$OCH_2), 3.43 (2H, t, *J* = 7.7 Hz, CH_2OC$\underline{H}_2$CH_2), 1.67 (3H, dd, *J* = 5.7, 4.4 Hz, CHC$\underline{H}_3$), 1.51-1.62 (2H, m, alkyl H), 1.22-1.40 (6H, m, alkyl H), 0.88 (3H, t, *J* = 5.8 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 205.7 (C), 88.1 (CH), 86.5 (CH), 70.2 (CH_2), 69.3 (CH_2), 31.9 (CH_2), 29.9 (CH_2), 26.0 (CH_2), 22.8 (CH_2), 14.27 (CH_3), 14.20 (CH_3); Found (TOF MS) $[M+H]^+$ 169.1591, $C_{11}H_{21}O$ requires 169.1592; $[\alpha]_D^{20°C}$ = +40.1 (c = 1.02 in $CHCl_3$); CSP-GC (β-Dex, 100 °C, 35 cm s^{-1}) **(*R*)-206l** 22.6 min and **(*S*)-206l** 23.0 min.

Gold Catalysed Hydroalkoxylation Reactions

General procedure

Allene (0.14 mmol, 1.0 equiv.), alcohol nucleophile (1.4 mmol, 10.0 equiv.) and DMF (0.14 ml) were added to a vial and stirred at 0 °C. IPrAuCl (8.7 mg, 10 mol%) was added followed by AgOTf (3.6 mg, 10 mol%). The reaction mixture was stirred at 0 °C for 24 h. The crude mixture was then passed through two silica plugs and washed with Et_2O. The solution was washed with water and brine and the organic layer was dried over $MgSO_4$, then concentrated. The crude mixture was purified by column chromatography to yield products.

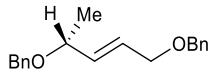
(*R*,*E*)-4-(Benzyloxy)pent-2-en-1-yl benzoate ((*R*)-195)[2]



General procedure followed on a 0.28 mmol scale and crude purified by column chromatography (eluent 20:1 hexane/EtOAc) to yield product **(*R*)-195** as a colourless oil (54.1 mg, 0.18 mmol, 65%, 98:2 e.r).

R_f 0.48 (5:1 hexane/EtOAc); ν_{max}/cm^{-1} 3031, 2973, 2864 (C-H), 1717 (C=O), 1601, 1584, 1494 (C-C Ar), 1268 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05-8.11 (2H, m, Ar-H), 7.54-7.61 (1H, m, Ar-H), 7.41-7.49 (2H, m, Ar-H), 7.26-7.37 (5H, m, Ar-H), 5.77-5.96 (2H, m, alkene-H), 4.85 (2H, d, *J* = 4.6 Hz, C$\underline{H}_2$OBz), 4.58 (1H, d, *J* = 11.9 Hz, PhC$\underline{H}_2$O), 4.43 (1H, d, *J* = 11.9 Hz, PhC$\underline{H}_2$O), 4.05 (1H, app. q, *J* = 6.3 Hz, BnOC$\underline{H}$CH$_3$), 1.32 (3H, d, *J* = 6.3 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 138.7 (C), 136.5 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.50 (CH), 128.49 (CH), 127.8 (CH), 127.6 (CH), 125.9 (CH), 75.1 (CH), 70.3 (CH_2), 64.8 (CH_2), 21.5 (CH_3); $[\alpha]_D^{21℃}$ = + 27.8 (c = 1.23 in $CHCl_3$); CSP-HPLC (Chiralcel OD-H, 99:1 hexane:IPA, 1 ml min^{-1}) **(*R*)-195** 11.5 min and **(*S*)-195** 15.2 min.

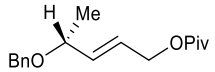
(*R*,*E*)-((Pent-2-ene-1,4-diylbis(oxy)bis(methylene))dibenzene ((*R*)-208)



General procedure followed on a 0.30 mmol scale and crude purified by column chromatography (eluent 25:1 hexane/EtOAc) to yield product **(*R*)-208** as a yellow oil (45%, 41 mg, 0.15 mmol, 95:5 e.r).

R_f 0.51 (5:1 hexane/EtOAc); ν_{max}/cm^{-1} 3063, 3029, 2973, 2855 (C-H), 1495, 1453, 1536 (C-C Ar), 1092 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23-7.40 (10H, m, Ar-H), 5.81 (1H, dt, *J* = 15.6, 5.1 Hz, CH=C<u>H</u>CH_2O), 5.67-5.77 (1H, m, C<u>H</u>=$CHCH_2O$), 4.58 (1H, d, *J* = 11.9 Hz, benzylic CH_2), 4.55 (2H, s, benzylic CH_2), 4.41 (1H, d, *J* = 11.9 Hz, benzylic CH_2), 4.07 (2H, d, *J* = 5.1 Hz, =CHC<u>H</u>$_2$O), 3.99 (1H, app. qn, *J* = 6.5 Hz, BnOC<u>H</u>CH_3), 1.31 (3H, d, *J* = 6.5 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 138.9 (C), 138.4 (C), 135.2 (CH), 128.54 (CH), 128.47 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 75.3 (CH), 72.3 (CH_2), 70.3 (CH_2), 70.2 (CH_2), 21.6 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 300.1957, $C_{19}H_{26}O_2N$ requires 300.1958. $[\alpha]_D^{21℃}$ = +35.8 (c = 0.95, $CHCl_3$); CSP-HPLC (ChiralPak IC, 99.3:0.7 hexane:IPA, 0.5 ml min^{-1}) **(*S*)-208** 12.8 min and **(*R*)-208** 14.9 min.

(*R*,*E*)-4-(Benzyloxy)pent-2-en-1-yl pivalate ((*R*)-207al)

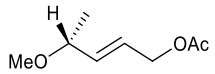


General procedure followed and crude purified by column chromatography (eluent 20:1 hexane/EtOAc) to yield product **(*R*)-207al** as a yellow oil (27.1 mg, 0.10 mmol, 70%, 93:7 e.r). e.r determined using ^{1}H NMR analysis with chiral shift reagent (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluroethanol on 400 MHz NMR, peak ~ 4.40 ppm.

R_f 0.24 (20:1 hexane/EtOAc); ν_{max}/cm^{-1} 3030, 2972, 2869 (C-H), 1727 (C=O), 1496, 1479, 1454 (C-C Ar), 1147 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.38 (5H, m, Ar-H), 5.73-5.81 (1H, m, CH=C<u>H</u>CH_2O), 5.70 (1H, dd, *J* = 16.5, 5.5 Hz, C<u>H</u>=$CHCH_2O$), 4.60 (2H, d, *J* = 5.5 Hz, =CHC<u>H</u>$_2$O), 4.56 (1H, d, *J* = 11.9 Hz, PhC<u>H</u>$_2$O), 4.40 (1H, d, *J* = 11.9 Hz, PhC<u>H</u>$_2$O), 3.97 (1H, app. qn, *J* = 6.4 Hz, BnOC<u>H</u>CH_3), 1.29 (3H, d, *J* = 6.4 Hz, CH_3), 1.23 (9H, s, ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 178.3 (C), 138.7 (C), 135.8 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 126.3 (CH), 75.0 (CH), 70.1 (CH_2), 64.1

(CH_2), 38.9 (C), 27.3 (CH_3), 21.5 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 294.2062, $C_{17}H_{28}O_3N$ requires 294.2064. $[\alpha]_D^{21℃}$ = +16.5 (c = 0.97, $CHCl_3$).

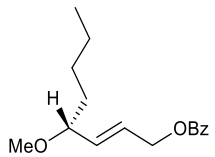
(*R*,*E*)-4-Methoxypent-2-en-1-yl acetate ((*R*)-207bn)



General procedure followed to yield product **(*R*)-207bn** as a colourless oil (16.9 mg, 0.11 mmol, 78%, 93:7 e.r). e.r determined using ^{1}H NMR analysis with chiral shift reagent (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluroethanol on 400 MHz NMR, peak 3.24 ppm.

ν_{max}/cm^{-1} 2974, 2932, 2820 (C-H), 1741 (C=O), 1447 (C-C Ar), 1097 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, dt, *J* = 15.8, 5.7 Hz, =C<u>H</u>CH_2O), 5.64 (1H, m, CHC<u>H</u>=CHCH_2), 4.56 (2H, d, *J* = 5.7 Hz, =CHC<u>H</u>$_2$O), 3.75 (1H, app. qn, *J* = 6.6 Hz, MeOC<u>H</u>CH=CH), 3.24 (3H, s, OMe), 2.07 (3H, s, O=CCH_3), 1.23 (3H, d, *J* = 6.4 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 170.9 (C), 136.2 (CH), 125.8 (CH), 77.4 (CH), 64.4 (CH_2), 56.2 (CH_3), 21.10 (CH_3), 21.09 (CH_3); Found (FTMS p CI) $[M + NH_4]^+$ 176.1, $C_8H_{18}O_3N$ requires 176.1; $[\alpha]_D^{21℃}$ = +18.4 (c = 1.09, $CHCl_3$).

(*R*,*E*)-4-Methoxyoct-2-en-1-yl benzoate ((*R*)-207cl)

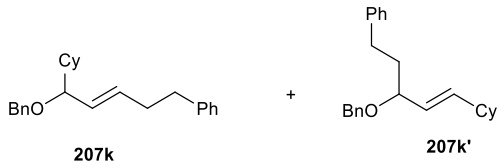


General procedure followed to yield product **(*R*)-207cl** as a colourless oil (34.6 mg, 0.13 mmol, 91%, 97:3 e.r).

ν_{max}/cm^{-1} 2930, 2859 (C-H), 1719 (C=O), 1602, 1451 (C-C Ar), 1097 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04-8.09 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.41-7.48 (2H, m, Ar-H), 5.86 (1H, dtd, *J* = 15.6, 5.8, 0.5 Hz, =C<u>H</u>CH_2O), 5.69 (1H, ddt, *J* = 15.6, 7.4, 1.1 Hz, MeOCHC<u>H</u>=CH), 4.83 (2H, dd, *J* = 5.8, 1.1 Hz, =CHC<u>H</u>$_2$O), 3.57 (1H, app. q, *J* = 6.8 Hz, MeOC<u>H</u>CH=CH), 3.28 (3H, s, OMe), 1.53-1.67 (1H, m, alkyl-H), 1.21-1.43 (7H, m, alkyl-H), 0.88 (3H, t, *J* = 6.9 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 135.3 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.5 (CH), 126.7 (CH), 81.9 (CH), 64.8 (CH_2), 56.5 (CH_3), 35.4 (CH_2), 31.9 (CH_2), 25.1 (CH_2), 22.7 (CH_2), 14.2 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 294.2064, $C_{17}H_{28}O_3N$ requires 294.2064;

$[\alpha]_D^{20^\circ C}$ = +7.3 (c = 1.09, $CHCl_3$); CSP-HPLC (ChiralPak IC, 99.3:0.7 hexane:IPA, 1 ml min^{-1}) **(*R*)-207cl** 9.5 min and **(*S*)-207cl** 9.7 min.

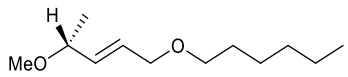
(*E*)-(5-(Benzyloxy)-5-cyclohexylpent-3-en-1-yl) benzene (207k)



General procedure followed and crude purified by column chromatography (eluent: 25:1 hexane/ether) to yield products **207k** and **207k'** as a colourless oil (32.6 mg, 0.10 mmol, 72%) in a 1:0.7 ratio.

R_f 0.43 (20:1 hexane/Et_2O); ν_{max}/cm^{-1} 3062, 3026, 2921, 2850 (C-H), 1603, 1495, 1451 (C-C Ar), 1093 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.03-7.42 (10H + 10H', m, Ar-H, major + minor), 5.42-5.55 (1H + 1H', m, alkene H, major + minor), 5.24-5.29 (1H, m, alkene-H, major), 5.18-5.24 (1H', m, alkene-H, minor), 4.50 (1H', d, *J* = 11.9 Hz, PhC$\underline{H}_2$O, minor), 4.40 (1H, d, *J* = 12.1 Hz. PhC$\underline{H}_2$O, major), 4.25 (1H', d, *J* = 11.9 Hz, PhC$\underline{H}_2$O, minor), 4.10 (1H, d, *J* = 12.1 Hz. PhC$\underline{H}_2$O, major), 3.61 (1H', app. q, *J* = 6.23 Hz, OC$\underline{H}$CH=CH, minor), 3.26, (1H, app t, *J* = 7.4 Hz, OC$\underline{H}$CH=CH, major), 2.51-2.73 (2H + 2H', m, alkyl H, major + minor), 2.30-2.40 (2H, m, alkyl H, major), 1.80-2.00 (1H + 2H', m, alkyl H, major + minor), 1.49-1.78 (5H + 5H', m, alkyl H, major + minor), 1.27-1.42 (1H + 1H', m, alkyl H, major + minor), 0.94-1.26 (2H + 5H', alkyl H, major + minor), 0.7-0.9 (2H, m, alkyl H, major + minor); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 142.4 (C, minor), 141.8 (C, major), 140.7 (CH, minor), 139.4 (C, major), 139.2 (C, minor), 133.9 (CH, major), 130.5 (CH, major), 128.7 (CH, major), 128.6 (CH, minor), 128.5 (CH, minor), 128.44 (CH, major), 128.40 (CH, minor), 128.3 (CH, minor), 128.0 (CH, minor), 127.9 (CH, major), 127.8 (CH, major), 127.5 (CH, minor), 127.3 (CH, major), 126.0 (CH, major), 125.8 (CH, minor), 84.8 (CH, major), 79.7 (CH, minor), 69.79 (CH_2, major), 69.77 (CH_2, minor), 42.7 (CH, major), 40.6 (CH, minor), 37.6 (CH_2, minor), 35.9 (CH_2, major), 34.1 (CH_2, major), 33.2 (CH_2, major), 33.1 (CH_2, minor), 31.9 (CH_2, minor), 29.5 (CH_2, major + minor), 29.2 (CH_2, major + minor), 26.8 (CH_2, major), 26.3 (CH_2, major), 26.2 (CH_2, minor), 26.1 (CH_2, minor); Found (FTMS p NSI+) $[M + NH_4]^+$ 352.2636, $C_{24}H_{34}ON$ requires 352.2635.

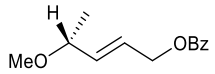
(*R*,*E*)-1-((4-Methoxypent-2-en-1-yl)oxy)hexane ((*R*)-207ln)



General procedure followed to yield product **(*R*)-207ln** as a colourless oil (26.8 mg, 0.13 mmol, 94%, 87:13 e.r).

ν_{max}/cm^{-1} 2956, 2929, 2855 (C-H), 1103 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (1H, dtd, *J* = 15.6, 5.7, 0.6 Hz, =C<u>H</u>CH$_2$O), 5.58 (1H, ddt, *J* = 15.6, 7.1, 1.1 Hz, CHC<u>H</u>=CHCH$_2$), 3.97 (2H, dd, *J* = 5.7, 1.1 Hz =CHC<u>H</u>$_2$O), 3.73 (1H, app. qn, *J* = 6.5 Hz, MeOC<u>H</u>CH=CH), 3.41 (2H, t, *J* = 6.7 Hz, CH$_2$OC<u>H</u>$_2$CH$_2$), 3.27 (3H, s, OMe), 1.52-1.63 (2H, m, alkyl H), 1.25-1.37 (6H, m, alkyl H), 1.23 (3H, d, *J* = 6.5 Hz, MeOCHC<u>H</u>$_3$), 0.88 (3H, t, *J* = 6.7 Hz, CH$_2$C<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 134.4 (CH), 129.0 (CH), 77.6 (CH), 70.9 (CH_2), 70.6 (CH_2), 56.1 (CH_3), 31.8 (CH_2), 29.9 (CH_2), 26.0 (CH_2), 22.8 (CH_2), 21.3 (CH_3), 14.2 (CH_3); Found (FTMS p NSI) $[M + NH_4]^+$ 218.2114, $C_{12}H_{28}O_2N$ requires 218.2115; $[\alpha]_D^{21^\circ C}$ = +22.5 (c = 1.07, $CHCl_3$) +22.5; CSP-GC (β-Dex, 80 °C, 35 cm s^{-1}) **(*R*)-207ln** 125.2 min and **(*S*)-207ln** 127.8 min.

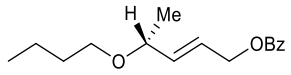
(*R*,*E*)-4-Methoxypent-2-en-1-yl benzoate ((*R*)-211n)



General procedure followed to yield product **(*R*)-211n** as a colourless oil (25.2 mg, 0.11 mmol, 81%, >95:5 e.r). E.r determined using ^{1}H NMR analysis with chiral shift reagent (*R*)-(-)-1-(9-anthryl)-2,2,2-trifluroethanol on 400 MHz NMR, peak 3.29 ppm.

ν_{max}/cm^{-1} 2974, 2930, 2820 (C-H), 1717 (C=O), 1601, 1584, 1451 (C-C Ar), 1097 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.08 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 7.0, 1.3 Hz, Ar-H), 7.40-7.48 (2H, m, Ar-H), 5.87 (1H, dtd, *J* = 15.6, 5.7, 0.7 Hz, CH=C<u>H</u>CH$_2$O), 5.74 (1H, ddt, *J* = 15.6, 6.7, 0.9 Hz, C<u>H</u>=CHCH$_2$O), 4.80-4.85 (2H, m, Ar-H), 3.78 (1H, app, qn, *J* = 6.7 Hz, MeOC<u>H</u>CH=CH), 3.29 (3H, s, OMe), 1.26 (3H, d, *J* = 6.7 Hz, CHC<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 136.2 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.5 (CH), 125.9 (CH), 77.3 (CH), 64.8 (CH_2), 56.2 (CH_3), 21.1 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 238.1438, $C_{13}H_{20}O_3N$ requires 238.1438; $[\alpha]_D^{21^\circ C}$ = +17.6 (c = 1.02, $CHCl_3$).

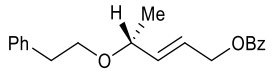
(*R*,*E*)-4-Butoxypent-2-en-1-yl benzoate ((*R*)-211p)



General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/ether) to yield product **(*R*)-211p** as a colourless oil (25.1 mg, 0.09 mmol, 68%, 97.5:2.5 e.r).

R_f 0.32 (10:1 hexane/Et_2O); ν_{max}/cm^{-1} 2958, 2931, 2869 (C-H), 1718 (C=O), 1601, 1584, 1451 (C-C Ar), 1094 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.09 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.41-7.48 (2H, m, Ar-H), 5.84 (1H, dt, *J* = 15.7, 5.4 Hz, CH=C<u>H</u>CH_2O), 5.78 (1H, dd, *J* = 15.7, 6.4 Hz, C<u>H</u>=$CHCH_2O$), 4.82 (2H, d, *J* = 5.4 Hz, CH=$CHC\underline{H}_2O$), 3.87 (1H, app. qn, *J* = 6.4 Hz, OC<u>H</u>CH=CH), 3.44 (1H, dt, *J* = 9.2, 6.6 Hz, $CH_2C\underline{H}_2O$), 3.33 (1H, dt, *J* = 9.2, 6.6 Hz, CH_2CH_2O), 1.49-1.60 (2H, m, ^{n}Bu-H), 1.32-1.44 (2H, m, ^{n}Bu-H), 1.25 (3H, d, *J* = 6.4 Hz, $OCHC\underline{H}_3$), 0.91 (3H, t, *J* = 7.3 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 137.0 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.5 (CH), 125.1 (CH), 75.6 (CH), 68.4 (CH_2), 64.9 (CH_2), 32.2 (CH_2), 21.4 (CH_3), 19.5 (CH_2), 14.1 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 280.1907, $C_{16}H_{26}O_3N$ requires 208.1907; $[\alpha]_D^{20^\circ C}$ = +15.6 (c = 1.02, $CHCl_3$); CSP-HPLC (ChiralPak IA, 99:1 hexane:IPA, 1 ml min^{-1}) **(*S*)-211p** 8.7 min and **(*R*)-211p** 9.7 min.

(*R*,*E*)-4-Phenylethoxypent-2-en-1-yl benzoate ((*R*)-211a)

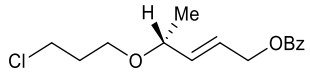


General procedure followed and crude purified by column chromatography (eluent 7:1 hexane/ether) to yield product **(*R*)-211a** as a colourless oil (27.1 mg, 0.08 mmol, 62%, 98:2 e.r).

R_f 0.40 (5:1 hexane/Et_2O); ν_{max}/cm^{-1} 3027, 2930, 2863 (C-H), 1716 (C=O), 1601, 1584, 1451 (C-C Ar), 1094 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95-8.00 (2H, m, Ar-H), 7.49 (1H, tt, *J* = 6.5, 1.3 Hz, Ar-H), 7.33-7.40 (2H, m, Ar-H), 7.10-7.22 (5H, m, Ar-H), 5.75 (1H, dt, *J* = 15.6, 5.2 Hz, CH=C<u>H</u>CH_2O), 5.66 (1H, dd, *J* = 15.6, 6.3 Hz, C<u>H</u>=$CHCH_2O$), 4.72 (2H, d, *J* = 5.2 Hz, CH=$CHC\underline{H}_2O$), 3.82 (1H, app. qn, *J* = 6.3 Hz, OC<u>H</u>CH=CH), 3.59 (1H, dt, *J* = 9.2, 7.5 Hz, $PhCH_2C\underline{H}_2O$), 3.48 (1H, dt, *J* = 9.2, 7.5 Hz, $PhCH_2C\underline{H}_2O$), 2.80 (2H, t, *J* = 7.5 Hz, $PhC\underline{H}_2CH_2O$), 1.18 (3H, d, *J* = 6.3 Hz, $OCHC\underline{H}_3$); ^{13}C NMR (75.5

MHz, $CDCl_3$) δ 166.4 (C), 139.1 (C), 136.7 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 129.1 (CH), 128.5 (CH), 128.4 (CH), 126.3 (CH), 125.4 (CH), 75.9 (CH), 69.8 (CH_2), 64.8 (CH_2), 36.7 (CH_2), 21.3 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 328.1907, $C_{20}H_{26}O_3N$ requires 328.1907; $[\alpha]_D^{20°C}$ = +23.2 (c = 0.95, $CHCl_3$); CSP-HPLC (ChiralPak IC, 99:1 hexane:IPA, 1 ml min^{-1}) **(*S*)-211a** 15.6 min and **(*R*)-211a** 18.0 min.

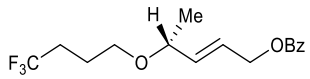
(*R*,*E*)-4-(3-Chloropropoxy)pent-2-en-1-yl benzoate ((*R*)-211q)



General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/ether) to yield product **(*R*)-211q** as a colourless oil (23.2 mg, 0.08 mmol, 60%, 97:3 e.r).

R_f 0.27 (10:1 hexane/Et_2O); ν_{max}/cm^{-1} 2971, 2868 (C-H), 1717 (C=O), 1601, 1451 (C-C Ar), 1097 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04-8.10 (2H, m, Ar-H), 7.57 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.40-7.49 (2H, m, Ar-H), 5.82-5.92 (1H, dtd, *J* = 15.6, 5.7, 0.5 Hz, CH=C<u>H</u>CH_2O), 5.72-5.80 (1H, ddt, *J* = 15.6, 6.7, 0.9 Hz, C<u>H</u>=$CHCH_2O$), 4.82 (2H, d, *J* = 5.7 Hz, CH=CHC<u>H</u>$_2$O), 3.90 (1H, app. qn, *J* = 6.6 Hz, OC<u>H</u>CH=CH), 3.64 (2H, t, *J* = 6.5 Hz, ClC<u>H</u>$_2CH_2$), 3.60 (1H, dt, *J* = 9.6, 5.9 Hz, CH_2C<u>H</u>$_2$O), 3.48 (1H, dt, *J* = 9.6, 5.9 Hz, CH_2C<u>H</u>$_2$O), 2.00 (2H, qn, *J* = 6.2 Hz, ClCH_2C<u>H</u>$_2CH_2O$), 1.25 (3H, d, *J* = 6.5 Hz, CH_3); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 136.5 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.5 (CH), 125.5 (CH), 75.9 (CH), 64.8 (2 x CH_2), 42.2 (CH_2), 33.0 (CH_2), 21.3 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 300.1362, $C_{15}H_{23}ClO_3N$ requires 300.1361; $[\alpha]_D^{19°C}$ = +16.3 (c = 0.98, $CHCl_3$); CSP-HPLC (ChiralPak IA, 98.8:1.2 hexane:IPA, 1 ml min^{-1}) **(*S*)-211q** 8.1 min and **(*R*)-211q** 11.2 min.

(*R*,*E*)-4-(4,4,4-Trifluorobutoxy)pent-2-en-1-yl benzoate ((*R*)-211r)

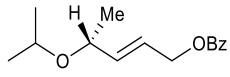


General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/ether) to yield product **(*R*)-211r** as a colourless oil (16.1 mg, 0.05 mmol, 37%, 99:1 e.r).

R_f 0.40 (5:1 hexane/Et_2O); ν_{max}/cm^{-1} 2975, 2868 (C-H), 1719 (C=O), 1601, 1585, 1451 (C-C Ar), 1096 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-8.09 (2H, m, Ar-H), 7.57 (1H,

tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.41-7.49 (2H, m, Ar-H), 5.84 (1H, dt, *J* = 15.6, 5.7 Hz, CH=C<u>H</u>CH$_2$O), 5.74 (1H, dd, *J* = 15.6, 6.7 Hz, C<u>H</u>=CHCH$_2$O), 4.82 (2H, d, *J* = 5.7 Hz, CH=CHC<u>H$_2$</u>O), 3.88 (1H, app. qn, *J* = 6.7 Hz, OC<u>H</u>CH=CH), 3.50 (1H, dt, *J* = 9.3, 6.2 Hz, CH$_2$C<u>H$_2$</u>O), 3.37 (1H, dt, *J* = 9.3, 6.2 Hz, CH$_2$C<u>H$_2$</u>O), 2.10-2.29 (2H, m, alkyl-H), 1.75-1.87 (2H, m, alkyl-H), 1.25 (3H, d, *J* = 6.7 Hz, CH$_3$); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 166.4 (C), 136.4 (CH), 133.1 (CH), 130.2 (C), 129.8 (CH), 129.2 (C, q, *J* = 279.8 Hz), 128.5 (CH), 125.7 (CH), 75.9 (CH), 66.6 (CH$_2$), 64.7 (CH$_2$), 31.1 (CH$_2$, q, *J* = 28.8 Hz), 22.7 (CH$_2$, q, *J* = 1.5 Hz), 21.3 (CH$_3$); Found (FTMS p NSI+) [M + NH$_4$]$^+$ 334.1624, C$_{16}$H$_{23}$F$_3$O$_3$N requires 334.1625; $[\alpha]_D^{20^\circ C}$ = +12.5 (c = 0.96, CHCl$_3$); CSP-HPLC (ChiralPak IA, hexane, 1 ml min^{-1}) **(*S*)-211r** 21.1 min and **(*R*)-211r** 26.3 min.

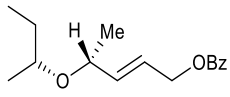
(*R*,*E*)-4-Isopropoxypent-2-en-1-yl benzoate ((*R*)-211m)



General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/ether) to yield product **(*R*)-211m** as a colourless oil (30.9 mg, 0.12 mmol, 88%, 97:3 e.r).

R$_f$ 0.24 (10:1 hexane/Et$_2$O); ν$_{max}$/cm^{-1} 2971 (C-H), 1719 (C=O), 1601, 1585, 1451 (C-C Ar), 1096 (C-O); ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.03-8.09 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.41-7.47 (2H, m, Ar-H), 5.85 (1H, dt, *J* = 15.6, 5.2 Hz, CH=C<u>H</u>CH$_2$O), 5.78 (1H, dd, *J* = 15.6, 5.5 Hz, C<u>H</u>=CHCH$_2$O), 4.81 (2H, d, *J* = 5.2 Hz, CH=CHC<u>H$_2$</u>O), 4.00 (1H, app. qn, *J* = 6.4 Hz, OC<u>H</u>CH=CH), 3.65 (1H, sept, *J* = 6.1 Hz, CH$_3$C<u>H</u>CH$_3$), 1.23 (3H, d, *J* = 6.4 Hz, CH$_3$), 1.15 (3H, d, *J* = 6.1 Hz, CH$_3$C<u>H</u>CH$_3$), 1.12 (3H, d, *J* = 6.1 Hz, CH$_3$C<u>H</u>CH$_3$); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ 166.4 (C), 137.6 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.5 (CH), 124.5 (CH), 72.6 (CH), 68.7 (CH), 65.0 (CH$_2$), 23.3 (CH$_3$), 22.1 (CH$_3$), 21.9 (CH$_3$); Found (FTMS p NSI+) [M + NH$_4$]$^+$ 266.1753, C$_{15}$H$_{24}$O$_3$N requires 266.1751; $[\alpha]_D^{20^\circ C}$ = +10.0 (c = 1.00, CHCl$_3$); CSP-HPLC (ChiralPak IA, 99:1 hexane:IPA, 0.5 ml min^{-1}) **(*S*)-211m** 13.3 min and **(*R*)-211m** 15.2 min.

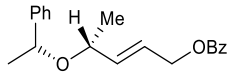
(*R*,*E*)-4-((*R*)-*sec*-Butoxy)pent-2-en-1-yl benzoate ((*R*)-211s)



General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/ether) to yield product **(*R*)-211s** as a colourless oil (28.3 mg, 0.11 mmol, 78%, 81:19 e.r).

R_f 0.33 (10:1 hexane/Et_2O); ν_{max}/cm^{-1} 2969, 2929, 2875 (C-H), 1719 (C=O), 1601, 1451 (C-C Ar), 1175 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.04-8.09 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.41-7.47 (2H, m, Ar-H), 5.76-5.90 (2H, m, alkene-H), 4.87 (2H, d, *J* = 4.1 Hz, CH=CHC$\underline{H}_2$O), 3.99 (1H, app. qn, *J* = 6.4 Hz, OC$\underline{H}$CH=CH), 3.41 (1H, sex, *J* = 6.1 Hz, $CH_3CH_2C\underline{H}CH_3$), 1.38-1.58 (2H, m, $CH_3C\underline{H}_2CHCH_3$), 1.25 (3H, d, *J* = 6.4 Hz, OCHC$\underline{H}_3$), 1.10 (3H, d, *J* = 7.2 Hz, $CH_3CH_2CHC\underline{H}_3$), 0.89 (3H, t, *J* = 7.4 Hz, $C\underline{H}_3CH_2CHCH_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 137.9 (CH), 133.1 (CH), 130.4 (C), 129.8 (CH), 128.5 (CH), 124.3 (CH), 74.5 (CH), 73.4 (CH), 65.0 (CH_2), 29.2 (CH_2), 21.6 (CH_3), 20.6 (CH_3), 9.9 (CH_3); Found (FTMS p NSI+) $[M + Na]^+$ 285.1458, $C_{16}H_{22}O_3Na$ requires 285.1461; $[\alpha]_D^{22^{\circ}C}$ = +8.5 (c = 0.47, $CHCl_3$); CSP-HPLC (ChiralPak IC, 99:1 hexane:IPA, 1 ml min^{-1}) **(*R*)-211s** 7.6 min and **(*S*)-211s** 10.2 min.

(*R*,*E*)-4-((*R*)-1-Phenylethoxy)pent-2-en-1-yl benzoate ((*R*)-211t)

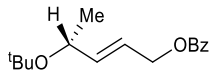


General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/ether) to yield product **(*R*)-211t** as a colourless oil (21.8 mg, 0.07 mmol, 51%, 97:3 e.r).

R_f 0.27 (10:1 hexane/Et_2O); ν_{max}/cm^{-1} 2973, 2928, 2875 (C-H), 1718 (C=O), 1584, 1492, 1450 (C-C Ar), 1175 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 7.97-8.03 (2H, m, Ar-H), 7.50 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.35-7.43 (2H, m, Ar-H), 7.16-7.29 (5H, m, Ar-H), 5.60-5.75 (2H, m, alkene-H), 4.76 (2H, dd, *J* = 4.3, 1.1 Hz, CH=CHC$\underline{H}_2$O), 4.43 (1H, q, *J* = 6.5 Hz, PhC$\underline{H}CH_3$), 3.68 (1H, app. qn, *J* = 6.4 Hz, OC$\underline{H}$CH=CH), 1.33 (3H, d, *J* = 6.5 Hz, PhCHC$\underline{H}_3$), 1.13 (3H, d, *J* = 6.4 Hz, OCHC$\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 144.2 (C), 136.5 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.5 (CH), 126.4 (CH), 125.7 (CH),74.7 (CH), 72.7 (CH), 64.8 (CH_2), 24.8 (CH_3),

22.0 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 328.1901, $C_{20}H_{26}O_3N$ requires 328.1907; $[\alpha]_D^{20℃}$ = +125.6 (c = 0.43, $CHCl_3$); CSP-HPLC (Chiralcel OD-H, 99:1 hexane:IPA, 1 ml min^{-1}) **(*R*)-211t** 35.4 min and **(*S*)-211t** 59.0 min.

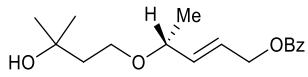
(*R*,*E*)-4,5,5-Trimethylhex-2-en-1-yl benzoate ((*R*)-211u)



General procedure followed and crude purified by column chromatography (eluent 10:1 hexane/ether) to yield product **(*R*)-211u** as a colourless oil (11.1 mg, 0.04 mmol, 30%, 94:6 e.r).

R_f 0.24 (10:1 hexane/Et_2O); ν_{max}/cm^{-1} 2973 (C-H), 1720 (C=O), 1601, 1451 (C-C Ar), 1175 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-8.07 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.40-7.47 (2H, m, Ar-H), 5.89-5.94 (1H, m, CH=C<u>H</u>CH_2O), 5.80 (1H, dd, *J* = 15.6, 0.9 Hz, C<u>H</u>=$CHCH_2O$), 4.80 (2H, d, *J* = 4.6 Hz, $CH=CHC\underline{H}_2O$), 4.17 (1H, app. qn, *J* = 6.4 Hz, OC<u>H</u>CH=CH), 1.22 (3H, d, *J* = 6.4 Hz, $OCHC\underline{H}_3$), 1.21 (9H, s, ^{t}Bu); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.5 (C), 139.9 (CH), 133.0 (CH), 130.5 (C), 129.8 (CH), 128.5 (CH), 122.6 (CH), 74.2 (C), 67.4 (CH), 65.3 (CH_2), 28.6 (CH_3), 23.5 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 280.1902, $C_{16}H_{26}O_3N$ requires 280.1907; $[\alpha]_D^{21℃}$ = +3.6 (c = 1.11, $CHCl_3$); CSP-HPLC (ChiralPak IA, 99:1 hexane:IPA, 1 ml min^{-1}) **(*S*)-211u** 6.8 min and **(*R*)-211u** 9.7 min.

(*R*,*E*)-4-(3-Hydroxy-3-methylbutoxy)pent-2-en-1-yl benzoate ((*R*)-211v)

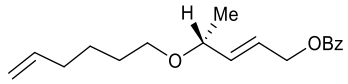


General procedure followed and crude purified by column chromatography (eluent 1:1 hexane/ether) to yield product **(*R*)-211v** as a colourless oil (24.2 mg, 0.08 mmol, 60%, 98.2 e.r).

R_f 0.25 (1:1 hexane/Et_2O); ν_{max}/cm^{-1} 3465 (O-H), 2970 (C-H), 1717 (C=O), 1601, 1584, 1451 (C-C Ar), 1095 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.03-8.09 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 6.5, 1.3 Hz, Ar-H), 7.40-7.47 (2H, m, Ar-H), 5.82-5.91 (1H, m, CH=C<u>H</u>CH_2O), 5.75 (1H, ddt, *J* = 15.6, 7.1, 1.0 Hz, C<u>H</u>=$CHCH_2O$), 4.81 (2H, d, *J* = 5.6 Hz, $CH=CHC\underline{H}_2O$), 3.89 (1H, app. qn, *J* = 6.5 Hz, OC<u>H</u>CH=CH), 3.72 (1H, dt, *J* = 9.5, 5.7 Hz, $CH_2C\underline{H}_2O$), 3.56 (1H, dt, *J* = 9.5, 5.7 Hz, $CH_2C\underline{H}_2O$), 3.36 (1H, br s, OH), 1.75

(2H, t, *J* = 5.7 Hz, HOCC<u>H</u>$_2$CH$_2$O), 1.27 (3H, d, *J* = 6.5 Hz, OCHC<u>H</u>$_3$), 1.23 (3H, s, HOCC<u>H</u>$_3$), 1.22 (3H, s, HOCC<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.3 (C), 135.9 (CH), 133.1 (CH), 130.2 (C), 129.8 (CH), 128.5 (CH), 126.1 (CH), 76.5 (CH), 70.6 (C), 65.9 (CH_2), 64.6 (CH_2), 41.5 (CH_2), 29.44 (CH_3), 29.42 (CH_3), 21.4 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 293.1749, $C_{17}H_{25}O_4N$ requires 293.1747; $[\alpha]_D^{20℃}$ = +20.6 (c = 0.58, $CHCl_3$); CSP-HPLC (ChiralPak IA, 97:3 hexane:IPA, 1 ml min^{-1}) **(*R*)-211v** 14.4 min and **(*S*)-211v** 16.0 min.

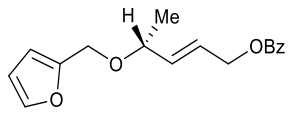
(*R*,*E*)-4-(Hex-5-en-1-yloxy)pent-2-en-1-yl benzoate ((*R*)-211w)



General procedure followed and crude purified by column chromatography (eluent 7:1 hexane/ether) to yield product **(*R*)-211w** as a colourless oil (26.9 mg, 0.09 mmol, 66%, 99.8:0.2 e.r).

R_f 0.20 (10:1 hexane/Et_2O); ν_{max}/cm^{-1} 2974, 2932, 2859 (C-H), 1719 (C=O), 1601, 1584, 1451 (C-C Ar), 1096 (C-O); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03-8.09 (2H, m, Ar-H), 7.56 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.40-7.49 (2H, m, Ar-H), 5.72-5.90 (3H, m, $CH_3CHC\underline{H}$=C$\underline{H}CH_2$ and CH_2=C$\underline{H}CH_2$), 4.90-5.04 (2H, m, C$\underline{H}_2$=CHCH_2), 4.82 (2H, d, *J* = 5.1 Hz, CH=CHC$\underline{H}_2$O), 3.87 (1H, app. qn, *J* = 6.4 Hz, OC$\underline{H}$CH=CH), 3.54 (1H, dt, *J* = 9.2, 6.7 Hz, $CH_2C\underline{H}_2$O), 3.33 (1H, dt, *J* = 9.2, 6.7 Hz, $CH_2C\underline{H}_2$O), 2.01-2.10 (2H, m, alkyl-H), 1.51-1.65 (2H, m, alkyl-H), 1.40-1.51 (2H, m, alkyl-H), 1.25 (3H, d, *J* = 6.4 Hz, OCHC<u>H</u>$_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 138.9 (CH), 137.0 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.5 (CH), 125.2 (CH), 114.6 (CH_2), 75.6 (CH), 68.5 (CH_2), 64.9 (CH_2), 33.7 (CH_2), 29.5 (CH_2), 25.7 (CH_2), 21.4 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 306.2065, $C_{18}H_{28}O_3N$ requires 306.2064; $[\alpha]_D^{21℃}$ = +16.1 (c = 0.99, $CHCl_3$); CSP-HPLC (ChiralPak IA, 97:3 hexane:IPA, 1 ml min^{-1}) **(*S*)-211w** 24.8 min and **(*R*)-211w** 34.0 min.

(*R*,*E*)-4-(Furan-2-ylmethoxy)pent-2-en-1-yl benzoate ((*R*)-211x)



General procedure followed and crude purified by column chromatography (eluent 5:1 hexane/ether) to yield product **(*R*)-211x** as a colourless oil (25.4 mg, 0.09 mmol, 64%, 99:1 e.r).

R_f 0.28 (5:1 hexane/Et_2O); ν_{max}/cm^{-1} 2974 (C-H), 1716 (C=O), 1601, 1584, 1451 (C-C Ar), 1069 (C-O); ^1H NMR (300 MHz, $CDCl_3$) δ 8.05-8.11 (2H, m, Ar-H), 7.57 (1H, tt, *J* = 6.5, 1.4 Hz, Ar-H), 7.42-7.48 (2H, m, Ar-H), 7.39 (1H, dd, *J* = 1.8, 0.9 Hz, furan-H), 6.32 (1H, dd, *J* = 3.2, 1.8 Hz, furan-H), 6.28 (1H, dd, *J* = 3.2, 0.9 Hz, furan-H), 5.90 (1H, dt, *J* = 16.1, 5.9 Hz, CH=C<u>H</u>CH_2O), 5.79 (1H, ddt, *J* = 16.1, 7.0, 1.1 Hz, C<u>H</u>=$CHCH_2O$), 4.84 (2H, dd, *J* = 5.9, 1.0 Hz, CH=$CHC\underline{H}_2O$), 4.50 (1H, d, *J* = 12.7 Hz, furan-$C\underline{H}_2O$), 4.37 (1H, d, *J* = 12.7 Hz, furan-CH_2O), 4.02 (1H, app. qn, *J* = 6.5 Hz, OC<u>H</u>CH=CH), 1.29 (3H, d, *J* = 6.5 Hz, $OCHC\underline{H}_3$); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 166.4 (C), 152.1 (C), 142.8 (CH), 136.0 (CH), 133.1 (CH), 130.3 (C), 129.8 (CH), 128.5 (CH), 126.2 (CH), 110.3 (CH), 109.2 (CH), 75.1 (CH), 64.7 (CH_2), 62.3 (CH_2), 21.4 (CH_3); Found (FTMS p NSI+) $[M + NH_4]^+$ 304.1543, $C_{17}H_{22}O_4N$ requires 304.1543; $[\alpha]_D^{22^\circ C}$ = +41.4 (c = 1.06, $CHCl_3$); CSP-HPLC (ChiralPak IA, 98:2 hexane:IPA, 1 ml min^{-1}) **(*R*)-211x** 6.56 min and **(*S*)-211x** 8.29 min.

6.7 References

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16 G.-J. Jiang, Q.-H. Zheng, M. Dou, L.-G. Zhuo, W. Meng and Z.-X. Yu, *J. Org. Chem.*, 2013, **78**, 11783.

Appendix

List of Publications

Dehydrative Thiolation of Allenols: Indium *vs* Gold Catalysis

S. Webster, P. C. Young, G. Barker, A. –L. Lee, *J. Org. Chem.,* **2015**, 80, 1703-1718

Gold Catalysed Proto- and Deuterodeboronation

G. Barker, S. Webster, D. G. Johnson, R. Curley, M. Andrews, P. C. Young, S. A. Macgregor, A. –L. Lee, *J. Org. Chem*., **2015**, 80, 9807

Indium *vs* Gold Catalysis in Dehydrative Reactions of Allylic Alcohols

S. Webster, L. Schaefer, G. Barker, A. –L. Lee, *SynLett*, **2015**, 26, 2673

Manuscripts in preparation

Iododeboronation of Boronic acids

S. Webster, C. Fletcher, A. –L. Lee

Chirality Transfer in the Hydroalkoxylation of 1,3-Disubstituted Allenes

S. Webster, D. Sutherland, A. –L. Lee